



The Efficacy of Hypnotic-Induced Prophylactic Naps for the Maintenance of Alertness and Performance in Sustained Operations

By

John A. Caldwell, Jr.
Roger W. Jones
J. Lynn Caldwell
Jose A. Colon
Andre Pegues
Lucinda Iverson
Kristi A. Roberts
Stephanie Ramspott
William D. Sprenger
Susan J. Gardner

Aircrew Health and Performance Division

February 1997

19970226 030

Approved for public release, distribution unlimited.

DTIC QUALITY INSPECTED 1

**U.S. Army Aeromedical Research Laboratory
Fort Rucker, Alabama 36362-0577**

Notice

Qualified requesters

Qualified requesters may obtain copies from the Defense Technical Information Center (DTIC), Cameron Station, Alexandria, Virginia 22314. Orders will be expedited if placed through the librarian or other person designated to request documents from DTIC.

Change of address

Organizations receiving reports from the U.S. Army Aeromedical Research Laboratory on automatic mailing lists should confirm correct address when corresponding about laboratory reports.

Disposition

Destroy this document when it is no longer needed. Do not return it to the originator.


Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation. Citation of trade names in this report does not constitute an official Department of the Army endorsement or approval of the use of such commercial items.

Human use

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Reg 70-25 on Use of Volunteers in Research.

Reviewed:

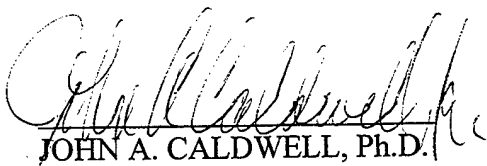


JEFFREY C. RABIN

LTC, MS

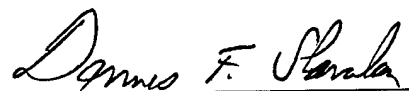
Director, Aircrew Health and
Performance Division

Released for publication:



JOHN A. CALDWELL, Ph.D.

Chairman, Scientific
Review Committee



DENNIS F. SHANAHAN

Colonel, MC, MFS
Commanding

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188		
1a. REPORT SECURITY CLASSIFICATION Unclassified			1b. RESTRICTIVE MARKINGS			
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release, distribution unlimited			
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE						
4. PERFORMING ORGANIZATION REPORT NUMBER(S) USAARL Report No. 97-10			5. MONITORING ORGANIZATION REPORT NUMBER(S)			
6a. NAME OF PERFORMING ORGANIZATION U.S. Army Aeromedical Research Laboratory		6b. OFFICE SYMBOL (If applicable) MCMR-UAD	7a. NAME OF MONITORING ORGANIZATION U.S. Army Medical Research and Materiel Command			
6c. ADDRESS (City, State, and ZIP Code) P.O. Box 620577 Fort Rucker, AL 36362-0577			7b. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21702-5012			
8a. NAME OF FUNDING / SPONSORING ORGANIZATION		8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER			
8c. ADDRESS (City, State, and ZIP Code)			10. SOURCE OF FUNDING NUMBERS			
			PROGRAM ELEMENT NO. 0602787A	PROJECT NO. 3M162787A879	TASK NO. OC	WORK UNIT ACCESSION NO. 175
11. TITLE (Include Security Classification) The efficacy of hypnotic-induced prophylactic naps for the maintenance of alertness and performance in sustained operations						
12. PERSONAL AUTHOR(S) J.A. Caldwell; R.W. Jones; J.L. Caldwell; J.A. Colon; A. Pegues; L. Iverson; et al.						
13a. TYPE OF REPORT Final		13b. TIME COVERED FROM TO		14. DATE OF REPORT (Year, Month, Day) 1997 February		
15. PAGE COUNT 63						
16. SUPPLEMENTAL NOTATION						
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)			
FIELD	GROUP	SUB-GROUP	Hynotics, naps, sleep deprivation, performance, mood, alertness, sustained operations			
19. ABSTRACT (Continue on reverse if necessary and identify by block number) <p>Army aviation units must be capable of sustained operations to achieve a tactical advantage over enemy forces. However, when adequate numbers of personnel are unavailable to staff all shifts, 24 hours per day, cognitive efficiency, mood, and motivation rapidly deteriorate because of insufficient sleep. A solution for this problem may be the implementation of a prophylactic napping strategy which allows personnel to store a limited amount of sleep prior to deprivation. Two hour naps have been shown to offer significant alertness benefits in sustained work periods.</p> <p>Unfortunately, although naps have been proven effective in the laboratory, there may be problems in operational situations. For instance, it may not be possible to place naps at times when sleep will be optimal. In these situations, it may be useful to facilitate napping with a short-acting sleep medication such as zolpidem tartrate. This should allow personnel to gain more restful sleep during limited time periods. However, there may be "hangover effects" since the half life of zolpidem is 2.5 hours.</p>						
20. DISTRIBUTION / AVAILABILITY OF ABSTRACT <input checked="" type="checkbox"/> UNCLASSIFIED/UNLIMITED <input type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified			
22a. NAME OF RESPONSIBLE INDIVIDUAL Chief, Science Support Center			22b. TELEPHONE (Include Area Code) (334) 255-6907		22c. OFFICE SYMBOL MCMR-UAX-SI	

19. Abstract, Continued

The present double-blind investigation examined the efficacy of prophylactic naps induced with zolpidem tartrate, in comparison to placebo naps and a forced-rest period, for sustaining the alertness of 18 Army aviators or flight students. Each subject received all three treatment interventions from 2100 to 2300 (13th-15th hour of sustained operations) on the evening prior to a night of sleep loss. Testing was conducted from 0100 until 2200 (17th-38th hour of sustained operations) the next day.

Results indicated prophylactic naps were beneficial in terms of sustaining mood, alertness, and performance throughout the final 24 hours of 38-hour periods of sustained operations. Self-ratings of vigor, alertness, energy, talkativeness, fatigue, irritability, and sleepiness all were improved by strategic napping in comparison to forced rest. Physiological indices demonstrated subjects were better able to remain awake after napping than after rest only. Also, there were electroencephalographic indications that central nervous system arousal was maintained more effectively by napping than by forced rest. Alertness decrements due to sleep loss were most severe between 0400 and 1000. Cognitive performance often, but not always, was impaired by sleep deprivation. Although subjects seemed to perform fuel management, desktop flight simulation, and auditory monitoring about as well when totally sleep deprived as after naps, they were better able to monitor systems, respond to warning lights, manage radios, track targets, and perform mental calculations after napping than after rest only, especially between 0700 and 1100.

Postnap grogginess was present for about 3 hours following naps (whether or not they were zolpidem induced). Although the benefits from napping later in the deprivation period appeared to outweigh the early postnap inertia, demanding operational tasks could be compromised if performed immediately following a nap. Future studies will be necessary to evaluate the impact of postnap sleep inertia on performance as well as mood.

The administration of zolpidem tartrate significantly increased the amount of sleep subjects obtained during the 2-hour napping periods. Subjects were able to go to sleep faster and remain asleep longer under drug than placebo, and they slept more soundly following zolpidem administration. These effects contributed to the superiority of the zolpidem nap in sustaining subsequent alertness. The advantages of this medication apparently were not offset by postnap side effects even though subjects were awakened 2.5 hours postdrug (which is the average half-life of zolpidem). However, it is clear that zolpidem should only be administered immediately prior to bedtime to avoid side effects (i.e., euphoria, grogginess, decrements in motor coordination) prior to sleep onset. Personnel who will receive zolpidem in the operational environment should be pretested prior to deployment because idiosyncratic reactions, such as hallucinations, can occur in some individuals.

Table of contents

	<u>Page</u>
Military Relevance	1
Objectives	1
Background	2
Naps and performance	2
Nap timing	2
Nap length	3
Nap placement and the circadian phase	3
Summary	5
Promoting Naps with Zolpidem Tartrate	5
General Characteristics	5
Pharmacokinetics	6
Safety	6
Adverse Reactions	6
Sleep architecture	7
Dosage	7
Factors affecting pharmacokinetics	7
Tolerance and Toxicity	8
Performance and hangover effects	8
Study Questions	8
Methods	9
Subjects	9
Apparatus	9
Personality evaluation	9
Mood evaluation	9
Sleepiness evaluations	10
Visual Analog Scale (VAS)	10
Repeated Test of Sustained Wakefulness (RTSW)	10
Cognitive evaluations	10
MATB	10
SYNWORK	10
Waking EEG evaluations	11
Desktop flight simulation task	11
Vital signs	11
Polysomnography	11

Table of contents (continued)

	<u>Page</u>
Procedure	11
Personality evaluation	12
Mood evaluation	12
Sleepiness evaluations	12
VAS	12
RTSW	12
Cognitive evaluations	12
MATB	12
SYNWORK	13
Waking EEG evaluation	13
Desktop flight simulation task	14
Vital signs	14
Polysomnography	14
Testing schedule	14
 Data Analysis	 15
 Results	 17
Personality evaluation	17
Mood evaluation	17
Sleepiness evaluations	18
VAS	18
Alertness	19
Energy	20
Confidence	21
Irritability	23
Jitteriness	24
Sleepiness	24
Talkativeness	25
RTSW	26
Cognitive evaluations	27
MATB	27
Resource management	28
Communications	28
Systems monitoring	30
Tracking	32
SYNWORK	32
Waking EEG evaluations	35
Delta	35

Table of contents (continued)

	<u>Page</u>
Theta	37
Alpha	38
Beta	39
Desktop flight simulation task	41
Vital signs	41
Polysomnography	43
Discussion	44
MMPI	44
Mood evaluation	45
Sleepiness evaluations	45
Cognitive evaluations	47
Waking EEG evaluation	49
Desktop flight simulation	50
Vital signs	50
Polysomnography	50
Side effects	51
Summary and conclusions	52
References	54
List of manufacturers	60

List of tables

1. Testing Schedule	16
---------------------------	----

List of figures

1. Personality profiles of the subjects used in this investigation compared to conventional Army aviators	17
2. Effects of the three conditions on POMS vigor scores	18
3. Effects of the three conditions on POMS fatigue ratings	19
4. Effects of time of day (with conditions collapsed) on POMS ratings	20
5. Effects of the three conditions on VAS alertness ratings	21
6. Effects of time of day (with condition collapsed) on VAS ratings	22
7. Effects of the three conditions on VAS energy ratings	23
8. Effects of the three conditions on VAS confidence ratings	23

List of figures (continued)

	<u>Page</u>
9. Effects of the three conditions on VAS irritability ratings	24
10. Effects of the three conditions on VAS sleepiness ratings	25
11. Effects of the three conditions on VAS talkativeness ratings	26
12. Effects of the three conditions on RTSW sleep latency	27
13. Effect of time of day (with conditions collapsed) on RTSW sleep latency	28
14. Effects of the three conditions on RT in the MATB communications task	29
15. Effects of time of day on mean RT, SDRT, and time-out errors in the MATB communications task	29
16. Effects of the three conditions on mean RT for lights, mean RT for dials, and SDRT for lights in the MATB systems monitoring task	30
17. Effects of time of day on performance of the MATB systems monitoring task . .	31
18. Effects of the three conditions on MATB tracking errors	32
19. Effects of time of day (with conditions collapsed) on MATB tracking errors	33
20. Effects of the three conditions on SYNWORK scores	33
21. Effects of time of day on SYNWORK arithmetic and auditory monitoring scores	34
22. Effects of the three conditions on SYNWORK visual monitoring scores	34
23. Effects of condition and eyes-open/eyes-closed on delta activity at Cz	35
24. Effects of condition and time of day on delta activity at Cz	36
25. Effect of time of day on delta activity at Fz	36
26. Effects of time of day and eye closure on theta activity at Fz, Cz, and C4	37
27. Effect of time of day on theta activity at Fz, Cz, C3, C4, and Pz	38
28. Effects of condition, time of day, and eye closure on alpha power at O1	38
29. Effects of time of day and eye closure on alpha activity at O1 and O2	39
30. Effects of condition and time of day on alpha activity at O1	40
31. Effects of the three conditions on alpha activity at O1 and O2	40
32. Effects of condition and eye closure on beta activity at O1	41
33. Effects of the three conditions on beta activity at C4, Pz, and O1	42
34. Effect of time of day on vital signs	43
35. Effects of the three conditions on polysomnographic measures	44

Military Relevance

To gain and maintain a tactical advantage on the modern battlefield, Army units must be capable of operating 24 hours per day for extended periods. Through such continuous operations, the strain upon enemy forces is maximized by requiring a sustained response from both equipment and personnel. However, unless the Army effectively manages all of its resources, the tactical advantage can be lost because of soldier fatigue and the resultant performance impairments.

The recent downsizing of U.S. military forces has led to increased concern that missions which were once effectively achieved by many soldiers are still required, but fewer soldiers now are available to accomplish them. Thus, individual soldiers are working longer hours, and units remain on alert for longer periods of time. This situation can eventually create significant problems unless work schedules, rest periods, and other factors are adequately managed.

Continuous operations present special challenges within the aviation community since pilots are responsible for planning missions, flying aircraft, managing flight personnel, and performing a host of other duties. Fatigue from long hours of work can lead to dangerous consequences for all concerned. Thus, appropriate countermeasures are required to ensure that aviators are sufficiently rested to perform their duties effectively.

One countermeasure is to offer pilots opportunities to take short naps prior to prolonged periods of continuous work. Research suggests that well-placed naps can sustain performance, but the positive effects of napping are influenced by many factors. In fact, in the operational environment, it may be necessary to use drug-induced naps in order to derive the expected performance benefits. However, additional research is necessary before practical guidance can be established.

Objectives

The first objective of this protocol was to determine whether a 2-hour nap taken by an aviator before a 40-hour mission without sleep would increase alertness, reduce fatigue, and mitigate the performance decrement normally associated with sleep deprivation. The second objective was to determine whether the nap's effectiveness would be enhanced by using a short-acting hypnotic (since in the real world, many factors such as anxiety, time of day, and noise may interfere with an aviator's ability to sleep when the opportunity arises). The third objective was to characterize the time course of any alertness or performance benefits derived from napping (both with and without the aid of a hypnotic). Cognitive performance, mood, sleepiness levels, and physiological parameters were measured to address each objective.

Background

Naps and performance

There is an abundance of evidence indicating that a nap taken during long periods of otherwise continuous wakefulness is extremely beneficial for improving alertness and performance (Akerstedt and Torsvall, 1985; Bonnet, 1990; 1991; Dinges et al., 1987; Dinges et al., 1988; Haslam, 1985; Lumley et al., 1986; Matsumoto and Harada, 1994; Mullaney et al., 1983; Naitoh and Angus, 1989; Naitoh, Englund, and Ryman, 1982; Rogers et al., 1989; Rosa, 1993; Webb, 1987). However, scheduling naps is not a simple matter. Several factors are important to consider before implementing a napping regime into a continuous operations scenario.

Nap timing

One important factor in scheduling naps is placing them at optimal times with regard to the amount of sleep loss. A review of the literature indicates that a nap taken during the day before an all-night work shift, with no sleep loss prior to the shift, will result in improved performance over the night compared to performance without the nap. Although naps taken later in the sleep-deprivation period also are beneficial, these naps probably should be longer than prophylactic naps in order to derive the same performance benefit. Schweitzer, Muehlback, and Walsh (1992) measured performance and alertness in subjects who received a 2- to 3-hour nap before a night work shift (with concurrent sleep loss). Although the usual circadian trough was seen in the early morning, the nap attenuated the decline in performance compared to a night where no nap was taken prior to the shift.

In a study conducted by Bonnet (1991), some subjects napped before a 52-hour continuous performance period while others remained awake. The nap was beneficial in keeping performance and alertness from decreasing for up to 24 hours of sleep loss as compared to the no-nap condition. However, by the second night of sleep loss, the benefit of the naps could not be reliably measured. In a study by Naitoh and colleagues (1982), subjects were given a 3-hour nap after being awake for approximately 24 hours. After the nap, they were required to stay awake an additional 20 hours. Results indicated that this 3-hour nap reduced the decline in performance during the additional work period. Other studies have found similar results using 24 hours of sleep deprivation (Dinges et al., 1987; Gillberg, 1984; Nicholson et al., 1985; Bonnet, 1990). In each case, naps taken prior to extended periods of sleep loss, "prophylactic naps," considerably attenuated the decrease in performance. The naps do not totally eliminate the circadian dip seen in the early morning (around 0500), but the degradation in both cognitive performance and alertness is attenuated compared to no napping conditions (Bonnet, 1990). These conclusions have received significant support

elsewhere (Mullaney et al., 1976; Gillberg, 1984; Nicholson et al., 1985; Carskadon & Dement, 1981; Haslam, 1985).

Nap length

Another factor to consider when scheduling naps during continuous operations is nap length. It is difficult to compare many of the nap studies due to variations in methodology; however, most studies indicate that naps from 1 hour to 8 hours will improve performance and alertness during continuous operations. A relationship between nap length and performance was reported by Bonnet (1991) based on a study in which subjects were allowed either a 2, 4, or 8-hour nap before 52 hours of continuous operations. The results indicated a dose-response relationship between the length of the nap and performance during the first 24 hours of sleep deprivation. Bonnet concluded that the nap before an all-night shift should be as long as possible to produce maximum performance benefits. He also concluded that prophylactic naps were better than naps designed to replace sleep that was already lost due to requirements for continuous wakefulness.

The importance of nap length was further highlighted in an investigation by Lumley and colleagues (1986), in which subjects were deprived of sleep for 24 hours and then permitted naps of either 15, 30, 60, or 120 minutes. The results indicated that alertness increased as a function of increased nap length, with the highest level of alertness occurring after the 60-minute nap. There was, however, no difference between the 60-minute nap and the 120-minute nap, possibly due to sleep fragmentation in the longer period.

Nap placement and the circadian phase

Another factor to consider when planning a napping strategy for use during continuous operations is where the nap should be placed in the circadian phase. This is a complicated issue because nap timing should take into account the ease of falling asleep at various times, the quality of sleep as a function of the body's internal clock, and the effects on performance both immediately after awakening and later in the work period. It has been established that sleep tendency is highest when core body temperature is in its trough, around 0300, and lowest when core body temperature is in its peak, around 1500 (Dinges, 1986). Thus, there may be significant problems initiating and/or maintaining a nap during times when core temperature is high. In part because of the potential impact of the temperature rhythm on sleep, Lavie (1986) considers the period from around 2000 to 2200 a "forbidden zone" for sleep, meaning that sleep initiation and maintenance are difficult during this time period (even in sleep-deprived personnel).

Naps which are placed during the circadian troughs are the easiest to maintain and they show beneficial effects on later performance. A study by Naitoh et al. (1982) indicated that a 3-hour nap taken between 0400 and 0700 (circadian trough) after 20 hours of continuous wakefulness reduced the amount of performance degradation seen upon awakening when compared to a no-nap group. When naps placed in the circadian trough are compared to naps placed in the circadian peak, the effects on performance are different. Gillberg (1984) examined the effects of a 1-hour nap placed either at 2100 or 0430 after 24 hours of sleep deprivation. Both naps improved performance the following morning when compared to a no-nap group, but the nap taken at 0430 (in the circadian trough) showed the most benefit. These findings, that early morning naps are most beneficial in restoring alertness and performance have been supported by others (Matsumoto, 1981; Naitoh et al., 1982).

Dinges and colleagues (1988) found that a nap taken anywhere in the circadian cycle before sleep deprivation will be beneficial in maintaining performance across the sleep loss period. However, there is a high cost to napping during the early morning (during the circadian trough). Although naps during the circadian trough may be more effective for performance sustainment (and although they are easier to initiate and maintain), they also are the more difficult naps from which to awaken. In fact, failure to account for the difficulty in awakening from these naps has caused some authors to initially conclude that naps during the circadian trough were inferior to naps placed elsewhere. For instance, Dinges et al. (1985) indicated that naps taken during the circadian trough are likely to be associated with lower performance than naps taken during circadian peaks--results which appear contrary to the general findings of other researchers. However, these conclusions were a result of the fact that Dinges et al. (1985) tested subjects immediately upon awakening, whereas other investigators allowed longer intervals of time to pass prior to task performance. Generally, studies have shown that post-nap sleepiness, termed "sleep inertia," is higher and performance is lower immediately upon awakening from a nap taken during the circadian trough as compared to naps taken during the circadian peak (Dinges, Orne, and Orne, 1985).

Lavie and Weler (1989) found that after 32 hours of sleep deprivation, a 2-hour nap taken at 1500 produced less sleep inertia than a 2-hour nap taken at 1900. However, the later nap was more successful in reducing early morning (2300 to 0400) sleepiness. Regardless of the time of the nap, sleep inertia will occur, and work requirements should be delayed accordingly. Performance generally will be lowest during the first 5 minutes after awakening, but it usually recovers after 15 to 30 minutes (Dinges et al., 1985). Generally, sleep inertia will be extended in situations where the timing of the nap is misplaced and/or the amount of sleep deprivation is extensive before the nap occurs. Thus, Dinges et al. (1985) suggest that during continuous operations, naps in the circadian trough should be avoided, and naps should be taken before a person's sleep loss extends beyond 36 hours. However, it should be possible to take advantage

of the improved quality of naps in the circadian trough while avoiding the sleep-inertia effects if napping personnel can be awakened about 1 hour prior to their work shifts.

Summary

In summary, the research concerning naps indicates that naps are beneficial for reducing sleepiness and performance decrements normally observed during sleep-deprivation periods. However, before scheduling naps during continuous operations, several factors should be taken into account. A nap is most beneficial if taken before significant sleep loss occurs (a prophylactic nap). This nap should be as long as possible, but even short naps can be beneficial. The timing of the nap should be planned in relation to the timing of work requirements. Sleep occurs most readily and performance is sustained most effectively when naps are placed in the circadian troughs; however, care must be taken to minimize the sleep inertia which is greatest when awakening from these naps. Therefore, when it is impossible to place a break between awakening and returning to work, naps should be placed during the circadian peak despite the fact that sleeping at this time will be more difficult and less restorative.

Promoting Naps with Zolpidem Tartrate

Unfortunately, scheduling naps for the operational environment is problematic because of mission demands and staff shortages. While it may be possible to place naps prior to sleep-deprivation periods and to maximize the duration of these naps, it may not be possible to schedule naps during times when personnel will find it easy to sleep (during circadian troughs). Even when it is predicted that personnel will have adequate time to recover from sleep inertia, it will not always be possible to place naps during the circadian trough. In addition, the anxiety, noise, heat, and environmental lighting present in operational scenarios may impair the ability of personnel to initiate and maintain effective prophylactic naps. Thus, it is necessary to provide a way for personnel to obtain needed sleep whenever the opportunity to sleep occurs. One possibility is to use a short-acting sleeping aid such as zolpidem tartrate which will quickly promote sleep, but will not produce hang-over effects which could interfere with performance.

General Characteristics

Zolpidem tartrate, marketed by G. D. Searle and Company as Ambien, is a non-benzodiazepine hypnotic of the imidazopyridine class. It is supplied in 5 and 10 mg tablets for oral administration (Physicians' Desk Reference, 1995). Zolpidem is not structurally similar to benzodiazepines (George, et al, 1988; Physicians' Desk Reference, 1995) which act on both BZ₁ and BZ₂ receptors of the Gamma-aminobutyric acid (GABA) receptor system. Zolpidem acts on the BZ₁ receptors at many of the same sites in the brain to produce hypnotic effects (Ascalone et al., 1992;

Langer et al., 1998). However, unlike benzodiazepines, it has been shown to have only weak anticonvulsant, motor performance, and myorelaxant effects (Merlotti et al., 1989). Also, daytime residual effects, common with some benzodiazepines, are almost absent following therapeutic doses of zolpidem (Blois et al., 1993).

The hypnotic effect of zolpidem has been clearly demonstrated in clinical trials (up to one year) in normal, elderly, and psychiatric patient populations with insomnia (Blois et al., 1993). Rebound insomnia, tolerance (treatment over 6-12 months), withdrawal symptoms, and drug interactions are absent, while dependence/abuse potential is low (Bartholini, 1988). The results of one study (Merlotti et al., 1989) showed that zolpidem did not produce rebound insomnia in any sleep parameters, even at the 20 mg dose, which is four times the active dose. Overall, zolpidem appears to be a clinically safe and useful hypnotic drug (Sanger et al., 1987; Palminteri and Narbonne, 1988) which is devoid of the adverse side-effects of the short-acting benzodiazepines.

Pharmacokinetics

Zolpidem tartrate is rapidly absorbed from the gastrointestinal (GI) tract, and it has a short elimination half-life in healthy subjects. The mean peak plasma concentration from 10 mg zolpidem tartrate tablets is 139 (se = 11.7) ng/ml⁻¹, occurring between 0.5 and 3.0 hours, with a mean of 1.03 hours (se = 0.2). The mean elimination half-life is 1.7 hours (se = 0.1) (Thenot et al., 1988). Zolpidem tartrate is metabolized in the liver with an overall bioavailability near 70 percent in man, and it has no active metabolites (Thenot et al., 1988).

Safety

Zolpidem tartrate has been studied extensively and has been shown to be safe in humans. In a dose-tolerance study, no serious side effects occurred in doses as high as 90 mg. With the 20 mg dose, side effects were minimal (Scharf et al., 1988). Generalization from studies conducted with lower animals indicates that the coefficient of safety is as high as 700 times the recommended therapeutic dose (Friedmann and Prenez, 1988). In studies conducted with rats and rabbits, no effects were found on fertility, and there was no teratogenic and/or embryotoxic potential, or peripostnatal problems (Friedmann and Prenez, 1988).

Adverse Reactions

The most common central and peripheral nervous system adverse reactions are headache, drowsiness, dizziness, lethargy, and a drugged feeling. The most common gastrointestinal reactions are nausea, dyspepsia, and diarrhea. Potential adverse respiratory system effects include upper respiratory infection, sinusitis, and pharyngitis (Palminteri and Narbonne, 1988; Physicians' Desk Reference, 1995). Although

memory disturbance is not common with zolpidem, it does occur and until the incidence of this effect is better characterized, some caution should be exercised. In the few cases in which anterograde amnesia was reported, it was not dose, sex, or age related, and most of the cases occurred after 2 weeks of treatment (mean = 31.6 days, median = 15 days, range = 0-150 days) (Palminteri and Narbonne, 1988).

Sleep architecture

In contrast to benzodiazepines, research indicates that low doses of zolpidem tartrate (10 mg or less) do not change the sleep architecture of normal sleepers (Blois et al., 1993; Merlotti et al., 1989). However, at doses higher than 10 mg (beyond the approved therapeutic dose), some changes in sleep stages have been found, mainly in stage 2 and slow wave sleep. Nicholson and Pascoe (1986) found a decrease in stage 2 and an increase in stage 3 with a 30 mg dose. Both stages 3 and 4 were increased with 20- and 30-mg doses.

Insomniacs and poor sleepers also show some changes in sleep architecture with zolpidem tartrate. Kryger et al. (1991) found the sleep of insomniacs manifested an increase in stage 2 and slow wave sleep, although the first postdrug night showed a return to baseline sleep levels. Other studies (Nicholson and Pascoe, 1986; Merlotti et al., 1989) have shown high doses of zolpidem tartrate (20 mg or higher) produced significant decreases in the percent of stage REM relative to placebo.

Dosage

The usual recommended dose of zolpidem tartrate for nonelderly adults is 10 mg given immediately before bedtime. However, evidence suggests that a dosage as low as 5 mg decreases sleep latency in some individuals (Lorizio et al., 1990).

Factors affecting pharmacokinetics

The incidence of various physiopathological factors and their effects on the pharmacokinetics of zolpidem tartrate have been investigated in a series of studies (Bianchetti et al., 1988). Age appears to have an effect on zolpidem tartrate's kinetics, and it is suggested that the initial dose be reduced to 5 mg in the elderly. It also has been observed that plasma concentrations of zolpidem are higher on the average in females than in males; however, this may be due to a difference in body weight and no change in dosage is recommended. Peak plasma concentration, peak time, or half life is not altered by time of administration. Food can reduce the rate and extent of gastrointestinal absorption, so sleep onset may be facilitated when taking the drug on an empty stomach. Neither alcohol nor caffeine altered pharmacokinetics; however, performance impairment was exacerbated by concurrent alcohol intake.

Tolerance and Toxicity

There is no evidence of tolerance during treatment or of rebound insomnia or withdrawal symptoms (Palminteri and Narbonne, 1988). Individuals who have ingested as much as 400 mg showed a full recovery. In cases of overdose, the Physicians' Desk Reference recommends immediate gastric lavage and the administration of intravenous fluids where appropriate. Respiration, pulse, and blood pressure should be monitored and general supportive measures employed. Flumazenil administration may be useful.

Performance and hangover effects

Most studies indicate that next-day performance is not affected by nighttime administration of 5 or 10 mg of zolpidem tartrate (Quera-Salva et al., 1994; Richens et al., 1993; Sicard et al., 1993). Higher dosages (20 mg) have been found to mildly affect next-day performance (Balkin et al., 1992), but even at this dosage, there have been few residual effects (Bensimon et al., 1990).

To date, only one study has investigated the usefulness of zolpidem tartrate (10 mg) for enhancing normal sleep periods during sustained operations (Sicard et al., 1993). In this study, one group of navy fighter pilots was given 10 mg at 2200 and the other group was given 10 mg at 0100. Both groups were then allowed to sleep prior to reporting for duty at 0730. Results indicated that zolpidem tartrate did not show residual effects on performance or mood in either group. There have been no systematic investigations of the use of zolpidem-induced naps for maintaining the performance of subjects in sustained-operations scenarios.

Study Questions

Since research indicates that taking a nap prior to sleep loss can help offset performance decrements seen during extended work schedules, it seems reasonable to consider napping to be a promising countermeasure for sleep loss in sustained operations. However, as mentioned earlier, there are optimal times during the 24-hour day in which naps occur more readily than others. Unfortunately, commanders may not be able to place naps at these optimal times, and regardless of the times during which naps are scheduled, aviators may not be able to sleep because of situational factors. Particularly in cases where the limited time available for a nap falls within the "forbidden zones" for sleep (Lavie, 1986), pharmacological measures may be necessary to promote restful sleep. This is where a very short-acting hypnotic such as zolpidem tartrate may be useful.

The first question addressed by this experiment was whether a 2-hour nap, placed late in the evening (during the "forbidden sleep zone") would affect the performance,

mood, and sleepiness of aviators during a continuous operations scenario. The second question was whether zolpidem tartrate could be effectively used to promote naps (and thus enhance the performance-sustaining effects of naps) during times when sleep was not expected to come readily.

Methods

Subjects

Eighteen subjects between the ages of 22 and 31 (mean=24.4) were recruited from Fort Rucker and other Army installations. Subjects were males (no females volunteered) who weighed between 145 and 205 pounds (mean=177.6 pounds). Fourteen of the subjects were flight students, and 4 were rated helicopter pilots. All subjects gave informed consent and were medically evaluated prior to testing. Subjects were healthy, nonsmokers who used only small amounts of caffeine (no more than three 8-ounce cups caffeinated coffee or five 12-ounce caffeinated soft drinks per day) and who reported no problems sleeping. Potential subjects were screened for current significant medical problems (including sleep abnormalities), use of tobacco products, current use of medications (other than sodium naproxin, ibuprophen, acetaminophen, or aspirin) that could not be discontinued, or excessive use of caffeine. Subjects were instructed to abstain from drug and alcohol use for 48 hours prior to the beginning of the study, and no drug or alcohol use was permitted during participation. Subjects remained inside of the U.S. Army Aeromedical Research Laboratory at Fort Rucker, Alabama for the duration of testing (10 consecutive days and 9 nights).

Apparatus

Personality evaluation

The Minnesota Multiphasic Personality Inventory (MMPI) was administered to characterize the personalities of the subjects used in this investigation. The MMPI (Form R) is a 566-item paper and pencil test which measures 10 personality factors: 1) hypochondriasis, 2) depression, 3) hysteria, 4) psychopathic-deviate, 5) masculinity-femininity, 6) paranoia, 7) psychasthenia, 8) schizophrenia, 9) hypomania, and 10) social introversion. There are also four validity scales. The answers were scored by computer. The results consisted of 14 scores (only the primary scales were examined), one for each factor.

Mood evaluation

The Profile of Mood States (POMS) (McNair, Lorr, and Droppleman, 1981) was used to assess subjective reports of mood at various times throughout the day. This

paper-and-pencil questionnaire consisted of 65 items which measured affect on 6 scales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The answers were scored by hand with scoring templates.

Sleepiness evaluations

Visual Analog Scale (VAS). Subjective sleepiness was measured via the VAS which consisted of eight 100 mm lines centered over the adjectives "alert/able to concentrate", "anxious", "energetic", "feel confident", "irritable", "jittery/nervous", "sleepy", and "talkative" (Penetar et al., 1993). At the extremes of each line, "not at all" and "extremely" were printed respectively. Scores consisted of the distance of the subject's mark from the left end of the line (in mm).

Repeated Test of Sustained Wakefulness (RTSW). Objective sleepiness was measured using the RTSW (Hartse, Roth, and Zorick, 1982) in which the subject's electroencephalogram (EEG) was recorded for up to 20 minutes using a Nihon Kohden electroencephalograph (Model No. EEG-4321P)* during the test to objectively determine whether or not he successfully remained awake (subjects were awakened and removed from the room immediately if they fell asleep). Records were scored in terms of the number of minutes from lights out until sleep onset (up to 20 minutes).

Cognitive evaluations

Two cognitive tests were administered -- the Multi-Attribute Test Battery (MATB) and the Synthetic Work Environment (SYNWORK), Version 2.0 (Elsmore, 1991). Both of these are computerized tests which were controlled by a 486 computer equipped with a standard keyboard, a joystick, and a mouse.

MATB. The MATB is a computerized aviation simulation test requiring subjects to perform an unstable tracking task while concurrently monitoring warning lights and dials, responding to auditory requests to adjust radio frequencies, and managing simulated fuel flow rates. Data on tracking errors, response times, time-outs, false alarms, and accuracy rates were calculated automatically by computer.

SYNWORK. The SYNWORK consists of a Sternberg memory task, an arithmetic task, a visual monitoring task, and an auditory monitoring task. These are presented simultaneously in four quadrants of the computer screen. Data on speed and accuracy were calculated automatically.

* See manufacturer's list

Waking EEG evaluations

Electroencephalograms (EEGs) were collected with a Cadwell Spectrum 32 neurometric analyzer.* The data from 7 active electrode sites (Fz, C3, Cz, C4, Pz, O1, and O2) referenced to linked mastoids (A1 and A2) were collected and stored on optical disk for future analysis. The low filter was set at 0.53 Hz, the high filter was set at 70 Hz, and the 60 Hz notch filter was used. Grass E5SH silver cup electrodes* were attached to each subject's scalp with collodion for the duration of the study.

Desktop flight simulation task

The desktop flight simulation task consisted of a custom-designed, timed flight course (via Microsoft Flight Simulator 4.0)* which was presented on a 486 computer with VGA graphics. Control of the flight was through a realistic flight yoke (Virtual Pilot, CH Products).* A total flight score was calculated automatically for each flight.

Vital signs

Oral temperatures were collected with an IVAC thermometer (Model number 811).* Pulse and blood pressure data were collected either with a Critikon vital signs monitor (Model number 1846SX)* or a conventional sphygmomanometer.

Polysomnography

Evaluations of sleep during naps and on baseline and recovery nights were made using a Nihon Kohden electroencephalograph, Model No. EEG-4321P.* The EEG data from electrodes C3, C4, O1, and O2, referenced to contralateral mastoids (A1 or A2), were recorded. Eye movements (EOG) were assessed with electrodes affixed to the outer canthus of each eye and referenced to A1. Muscle activity (EMG) was recorded from submental electrodes affixed with adhesive collars. The time constant for the EEG channels was 0.3 seconds, and the high filter was 35 Hz. For EOG, the time constant was 5.0 seconds, and the high filter was 10 Hz. For EMG, the time constant was 0.003 seconds, and the high filter was 120 Hz. The 60 Hz notch filter was used as necessary.

Procedure

During three sleep deprivation periods, each subject completed several test sessions which consisted of cognitive batteries, flight simulation, sleepiness and electrophysiological evaluations, and mood state questionnaires. Subjects were tested following a nap induced with zolpidem tartrate (Znap), a nap without zolpidem tartrate (Pnap), and a rest period with no nap (Nonap). The conditions were counter-balanced and the drug administration was double-blind. Subjects signed an informed consent before the study began.

Personality evaluation

The MMPI was given to each subject prior to the initiation of training and testing (with the exception of one subject who was tested on the last day). Subjects were given a test booklet with an answer sheet, and were told to follow the instructions inside of the test booklet. Subjects answered each of the questions in terms of how the feelings described usually applied to them. The test took approximately 1 hour.

Mood evaluation

The POMS was administered every 2 hours beginning at 0900 on training and control days and at 0100 on sleep deprivation days. The last administration occurred at 1900 on each day. The test was administered using the standard POMS answer sheet on which subjects indicated how well each of 65 adjectives described the way they were feeling at the time. The test took approximately 5 minutes.

Sleepiness evaluations

VAS. The VAS was administered every hour on the hour from 0900 to 2000 on training and control days, and from 0100 to 2000 on test days. In addition, there was a VAS immediately following the nap (or rest) periods (at 2300). The VAS was given before the cognitive batteries and before the RTSW. The subject was given a test sheet containing a series of 100 mm lines drawn horizontally over the adjectives described earlier. At the extremes of each line, "not at all" and "extremely" were printed respectively. The subject placed a mark on the line to indicate his present feelings.

RTSW. The RTSW occurred every 2 hours. Subjects were required to lie on a bed in a quiet, darkened room after being instructed as follows: "lie as still as possible with your eyes closed and do your best to remain awake." During the RTSW, EEG data were recorded from electrode sites C3, C4, O1, and O2, referenced to the contralateral mastoid. The subject was allowed to remain in bed either until 20 minutes had elapsed or until he entered stage 2 sleep (the first k complex or sleep spindle). The elapsed time from lights out until sleep onset was recorded.

Cognitive evaluations

MATB. Subjects completed the MATB every 4 hours from 0910 to 1710 on training and control days, and from 0110 to 1710 on test days. The test followed the completion of the POMS and VAS and was 30 minutes in length. Subjects were required to simultaneously monitor and respond to 4 different tasks throughout the testing period. As described earlier, there was a resource management task (monitoring fuel levels), a communications task (adjusting radio frequencies in response to verbal commands), a

systems monitoring task (monitoring lights and dials), and an unstable tracking task. In the *resource management task*, subjects were required to maintain 2500 units of "fuel" in two tanks by monitoring and controlling the status of 8 "pumps." The *communications task* required subjects to monitor verbal instructions about radio-frequency changes presented via headphones and respond only to the ones preceded by their unique call sign (NGT504). The *systems monitoring task* required subjects to attend to 2 warning lights and 4 dials and to press specific keys either to terminate the onset of a specific light or to reset a dial deviating more than 2 tick marks from center. The *tracking task* required subjects to center an unstable target in the middle of the top right quadrant of the computer screen. Scores on accuracy and speed were recorded automatically by computer.

SYNWORK. The SYNWORK was completed every 4 hours from 1105 to 1905 on training and control days, and from 0305 to 1905 on test days. This test required the subject to monitor four tasks presented simultaneously in different quadrants of the computer screen. The *Sternberg memory task*, in the upper left corner, presented the subject with six letters which were subsequently removed from view. Letters were then presented one at a time and the subject was required to indicate whether each letter was part of the initial six-letter set. A *three-column addition task*, presented in the upper right corner, required subjects to add two numbers totaling less than 1000. Responses were entered using a mouse-driven keypad. The *visual monitoring task*, presented in the lower left corner, entailed subjects watching a pointer which moved from the center to either end of the scale. The subject was required to reset the pointer before it moved to the end. An *auditory monitoring task* was presented in the lower right corner. The subject was required to respond when a high tone was presented among a series of low tones. All responses to each task were made via a mouse to avoid keyboard distractions. Each task was scored in terms of accuracy and speed.

Waking EEG evaluation

The electrophysiological evaluations lasted approximately 10 minutes. The sessions occurred every 4 hours from 1030 to 1830 on training and control days and from 0230 to 1830 on test days. The electrodes were checked before each session to ensure impedances were 5000 Ohms or less. Any problems were corrected by rotating a blunted needle gently in the electrode until the correct impedance was obtained. The subjects were seated in a comfortable chair in a sound-attenuated booth, where they were instructed to sit quietly with eyes open and fixated for 1.5 minutes followed by eyes closed for 1.5 minutes. The data from the resting EEG were visually scanned for 3 relatively artifact free 2.5-second epochs and fast Fourier transformations were conducted. The averaged epochs produced four power values for each electrode site under eyes closed and eyes open. The activity bands were delta (1.0-3.0 Hz), theta (3.0-8.0 Hz), alpha (8.0-13.0 Hz), and beta (13.0-20.0 Hz).

Desktop flight simulation task

The desktop flight simulator was performed every 4 hours from 1130 to 1930 on training and control days and from 0330 to 1930 on test days. Each session lasted approximately 30 minutes. The subject was required to fly a timed course which consisted of 21 "gates" positioned at various places on the course. The first 15 gates were flown with no turbulence and the last 6 gates were flown with 20-knot winds emanating from various directions. A summary score dependent on the elapsed time required to fly the course, the number of gates missed, and the precision of flying through the gates was calculated automatically by the program after each flight.

Vital signs

Oral temperatures, pulse rates, respiration rates, and blood pressures were collected every other waking hour. Measures were collected from 1000 to 2000 (and once again at 2300) on control days and from 0200 to 2135 on test days.

Polysomnography

EEG, EOG, and EMG were recorded each night the subject was allowed to sleep and during each of the 2-hour naps in order to assess sleep quality. Approximately 15 minutes before lights out, EOG and EMG electrodes were placed. The subjects then were escorted to private bedrooms where electrodes were plugged into the preamplifiers and signal quality was assessed. Afterwards, the lights were turned out and the subjects were permitted to sleep. The first night of sleep was Sunday night (the adaptation night). Monday night served as the baseline sleep night. Wednesday, Friday, and Sunday nights were recovery nights. Lights out on all of these nights was 2200. Subjects were allowed to sleep until 0800 the next morning, but were allowed to arise earlier if desired. Naps occurred from 2100 to 2300 on Tuesday, Thursday, and Saturday nights. All sleep data, including naps, were recorded on standard polygraph paper and were scored according to standard rules (Rechtschaffen and Kales, 1968). However, only the sleep architecture for the naps will be discussed in the present report. Naps were scored in terms of sleep latency (number of seconds from lights out to the first full minute of stage 2 sleep), percentage of time in each sleep stage, movement time, and time awake after sleep onset.

Testing schedule

Each subject reported to the laboratory on *Sunday* afternoon and signed the informed consent prior to medical records review. Completion of the MMPI and attachment of electrodes followed. Initial training was then conducted on several of the tests prior to the adaptation sleep period which began at 2200 on Sunday night. On *Monday*, there were three training sessions (at 0900, 1300, and 1700) during which

subjects completed all tests in the sequence to be used for the remaining 8 days. Within each session, the POMS, VAS and MATB were followed by the RTSW, electrophysiology evaluations, SYNWORK, and desktop flight simulator. There was an additional RTSW at the end of each session. Subjects slept from 2200-0800 on Monday night. On *Tuesday* (a control day), the schedule was the same except the subject was not permitted to sleep at night. Instead, he received the first of one of three interventions: 1) a 2-hour nap with 10 mg zolpidem tartrate (Znap), 2) a 2-hour nap with placebo (Pnap), or 3) a 2-hour rest period during which no sleep occurred (Nonap). Each intervention began at 2100 and ended at 2300. For the nap conditions, the drug or placebo was administered 30 minutes prior to lights out. This was done instead of giving the drug immediately prior to bedtime because for blinding purposes, the active drug was placed inside of a gelatin capsule which lengthened the absorption time (Searle would not provide matching placebo tablets for this investigation). After the drug was administered, electrode attachments (for EOG and EMG) were completed and subjects were escorted to a bedroom for a 2-hour nap. In the Nonap condition, subjects spent their time watching television and conversing with staff members (they were monitored at all times to ensure that no sleep occurred during the rest period). On *Wednesday* (a test day), the first post-intervention test session began at 0100 (2 hours after the nap or rest period) and subsequent sessions occurred every four hours (sessions started at 0100, 0500, 0900, 1300, and 1700). Subjects were allowed to sleep Wednesday night from 2200 to 0800. The schedule on *Thursday* and *Saturday* (control days) was the same as the one on Tuesday, and the schedule on *Friday* and *Sunday* (test days) was the same as the one on Wednesday. The *second Monday* of each subject's participation was a recovery day in which the control-day schedule (i.e., the one for Tuesday, Thursday, and Saturday) was followed. On the morning of the *second Tuesday*, subjects were evaluated and released. See Table 1 for a full schedule of each day's test sessions.

Data Analysis

The data collected from each independent measure (with the exception of the MMPI) were analyzed with a two-way repeated measures analysis of variance (ANOVA) for condition (Znap, Pnap, and Nonap) and time. The alpha level was set at .05. Huynh-Feldt corrected degrees of freedom were applied in the event of significant departures from the compound symmetry assumption. Significant interactions were followed up with analysis of simple effects, and main effects were assessed with pairwise contrasts among the means.

The data from the test days (following each of the three conditions) were analyzed for presentation in this report. Thus, only the information collected from subjects under conditions of sleep deprivation will be discussed. Data from the control days were examined as well to ensure that there were no systematic differences present which

may have confounded the effects of the napping conditions. However, the results of control-day ANOVAs are not reported since no systematic effects were found.

Table 1.
Testing Schedule

Time	Sunday	Monday Training	Tuesday Baseline	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday
0100				VAS/POMS		VAS/POMS		VAS/POMS		
0110				MATB		MATB		MATB		
0200				VAS/Vitals Elec Rep		VAS/Vitals Elec Rep		VAS/Vitals Elec Rep		
0205										
0210				RTSW		RTSW		RTSW		
0235				EEG/EP		EEG/EP		EEG/EP		
0300				VAS/POMS SYNWORK		VAS/POMS SYNWORK		VAS/POMS SYNWORK		
0310										
0330				Minisim		Minisim		Minisim		
0400				VAS/Vitals Elec Rep		VAS/Vitals Elec Rep		VAS/Vitals Elec Rep		
0405										
0410				RTSW		RTSW		RTSW		
0500				VAS/POMS		VAS/POMS		VAS/POMS		
0510				MATB		MATB		MATB		
0600				VAS/Vitals Elec Rep		VAS/Vitals Elec Rep		VAS/Vitals Elec Rep		
0605										
0610				RTSW		RTSW		RTSW		
0635				EEG/EP		EEG/EP		EEG/EP		
0700				VAS/POMS SYNWORK		VAS/POMS SYNWORK		VAS/POMS SYNWORK		
0730				Minisim		Minisim		Minisim		
0800		Wakeup	Wakeup	VAS/Vitals Elec Rep RTSW	Wakeup	VAS/Vitals Elec Rep RTSW	Wakeup	VAS/Vitals Elec Rep RTSW	Wakeup	Wakeup
0805										
0810										
0830		Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast
0900		VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	Debrief
0910										
1000		VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	Release
1005										
1010		RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	
1035		EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	
1100		VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	
1110										
1130		Minisim	Minisim	Minisim	Minisim	Minisim	Minisim	Minisim	Minisim	
1200		VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	
1210		RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	
1235		Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	
1300		VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	
1310		MATB	MATB	MATB	MATB	MATB	MATB	MATB	MATB	
1400		VAS/Vitals Elec Rep	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	
1405										
1410		RTSW								
1435		EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	
1500	Arrive/ Inservice	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	
1510										
1530	Inservice	Minisim	Minisim	Minisim	Minisim	Minisim	Minisim	Minisim	Minisim	
1600	Medicals 1635	VAS/Vitals Elec Rep	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	
1605										
1610		RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	
1700	Electrode Hook-up	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	
1710										
1800	Vitals/ Dinner	VAS/Vitals Elec Rep	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	Elec Rep/ VAS/RTSW	
1810										
1835		EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	
1900		VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	VAS/POMS SYNWORK	
1910										
1930		Minisim	Minisim	Minisim	Minisim	Minisim	Minisim	Minisim	Minisim	
2000		VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	VAS/Vitals Elec Rep	
2005										
2010		RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	RTSW	
2035		Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	
2100		PT	PT/Nap	PT	PT/Nap	PT	PT/Nap	PT	PT	
2130	Vitals	PT/Shower		PT/Shower		PT/Shower		PT/Shower	PT/Shower	
2205	Lights out	Lights out		Lights out		Lights out		Lights out	Lights out	
2300 (2330)			Wakeup/VAS/ Vitals (PT)		Wakeup/VAS/ Vitals (PT)		VAS			
2400			Shower/ Elec Rep		Shower/ Elec Rep		Shower/ Elec Rep			

Results

Personality evaluation

MMPI data were examined only for the purpose of helping to ensure the personality makeup of the present sample did not differ markedly from conventional Army aviators. Thus, MMPI data were simply described rather than subjected to hypothesis testing. As can be seen in figure 1, the group personality profile did not present evidence of any significant scale elevations (t scores greater than 70 or less than 30), and there were no marked differences between the scale scores obtained from this sample and those of conventional Army aviators (taken from archived laboratory data).

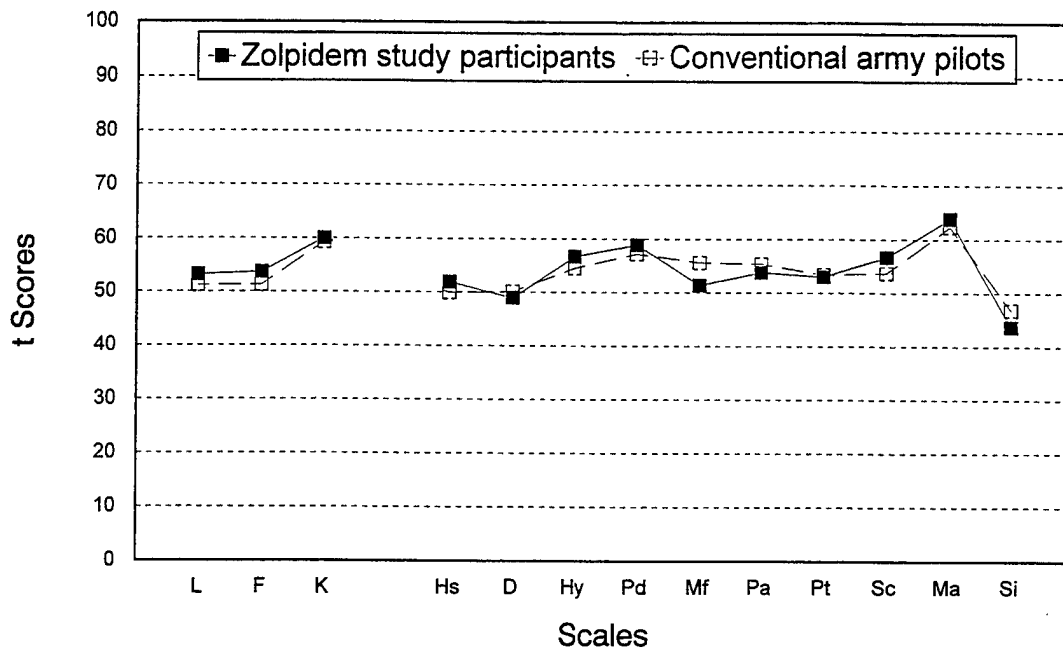


Figure 1. Personality profiles of the subjects used in this investigation compared to conventional Army aviators

Mood evaluation

The scores from each of the six scales of the POMS were analyzed in a 3 by 10 ANOVA with repeated measures on the condition (Znap, Pnap, and Nonap) and time (0100, 0300, 0500, 0700, 0900, 1100, 1300, 1500, 1700, and 1900) factors. The analysis revealed a significant condition-by-time interaction on vigor scores ($F(18,306)=2.05$, $p=.0075$) which was due to differences among the three conditions at 0500, 0700, and 1900 ($p<.05$). Contrasts indicated Znap was associated with higher vigor scores than Nonap at 0500 and 0700, while Pnap was better than Nonap only at 0700 ($p<.05$). At 1900, Pnap was better than both Znap and Nonap. These effects are depicted in figure 2.

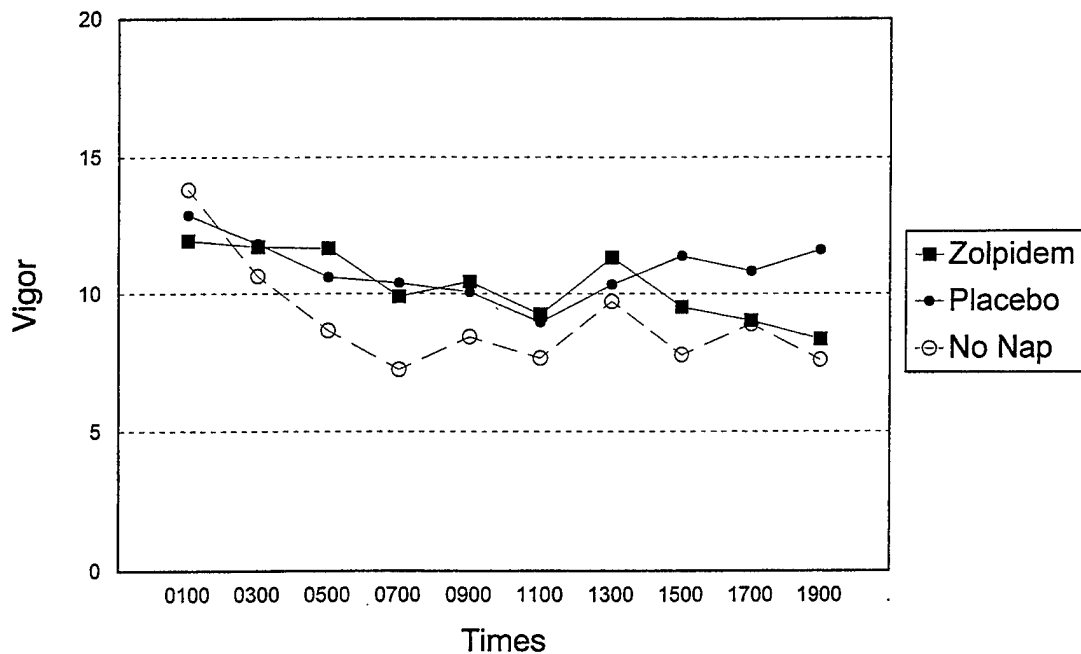


Figure 2. Effects of the three conditions on POMS vigor scores

A condition main effect was found on the fatigue scale ($F(2,16)=2.86$, $p=.0495$), due to lower overall fatigue ratings under Znap in comparison to Nonap ($p<.05$). As can be seen in figure 3, the other comparisons were not statistically significant. Time main effects were observed on ratings of tension ($F(9,153)=3.50$, $p=.0006$), depression ($F(9,153)=2.30$, $p=.0186$), vigor ($F(9,153)=6.14$, $p<.0001$), fatigue ($F(9,153)=9.20$, $p<.0001$), and confusion ($F(9,153)=5.87$, $p<.0001$). Generally speaking, these effects were due to deteriorations in mood from the early morning hours (i.e., 0100 or 0300) to approximately 1100. Afterwards, mood tended to improve slightly (from 1100 to 1300), and then decline once again as can be seen in figure 4.

Sleepiness evaluations

VAS

The scores obtained from the VAS were analyzed with a 3 X 21 repeated measures ANOVA for condition (Znap, Pnap, and Nonap) and time (immediately after each intervention, at 2300, and hourly from 0100 to 2000). The analysis indicated numerous interactions and main effects. These effects were examined further using analysis of simple effects and pairwise contrasts. Due to the excessive number of contrasts that would have been required across the time factor, only every other VAS from 0100 to 1900 was examined when the time main effect was significant.

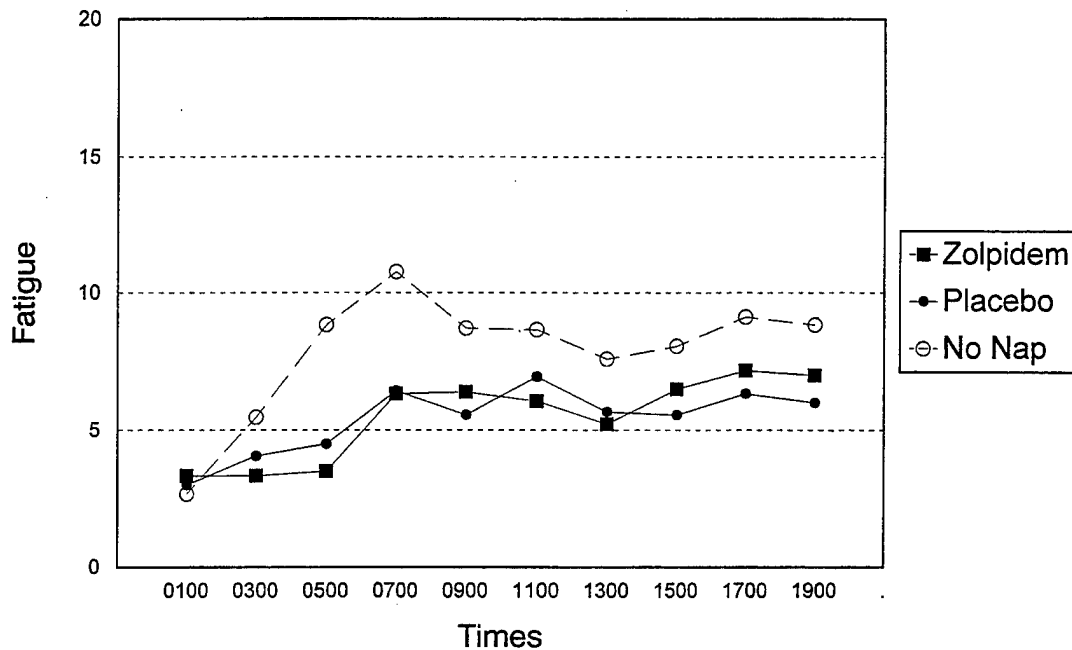


Figure 3. Effects of the three conditions on POMS fatigue ratings

Alertness. Alertness ratings were significantly affected by the combination of condition and time ($F(40,680)=4.35$, $p<.0001$), condition alone ($F(2,34)=4.36$, $p=.0206$), and time alone ($F(20,340)=4.52$, $p<.0001$). The interaction was due to differences among the three conditions at 2300, 0100, 0400, 0500, 0700, 0800, 0900, 1000, 1100, and 2000 ($p<.05$). At 2300 and 0100, alertness was lower after both Znap and Pnap in comparison to the Nonap condition, probably because of sleep inertia and some drug hangover upon awakening. At each of the remaining times, Znap was better than Nonap; and with the exception of 0500 and 2000, Pnap was better than Nonap. In addition, Znap was better than Pnap only at 0500 ($p<.05$). These effects are depicted in figure 5.

The condition main effect was attributable to higher alertness ratings after Znap than after Nonap ($p<.05$), but there were no differences between Pnap and the other conditions. The time main effect was due to a general reduction in alertness from 0100 until approximately 1100, after which there was a slight recovery between 1300 and 1700, followed by another drop towards the end of the day ($p<.05$). Specifically, the ratings at 0100 were higher than those from 0300-1900; the ratings at 0300 were higher than those at 0700, 0900, 1100, and 1500; and the ratings at 0500 were greater than those at 0900 or 1100. Conversely, the ratings at 0700 were lower than those at 1300 and 1700; the one at 0900 was lower than the one at 1700; and the rating at 1100 was lower than the ratings at 1300 and 1700. Finally, alertness ratings decreased from 1700 to 1900 as can be seen in figure 6.

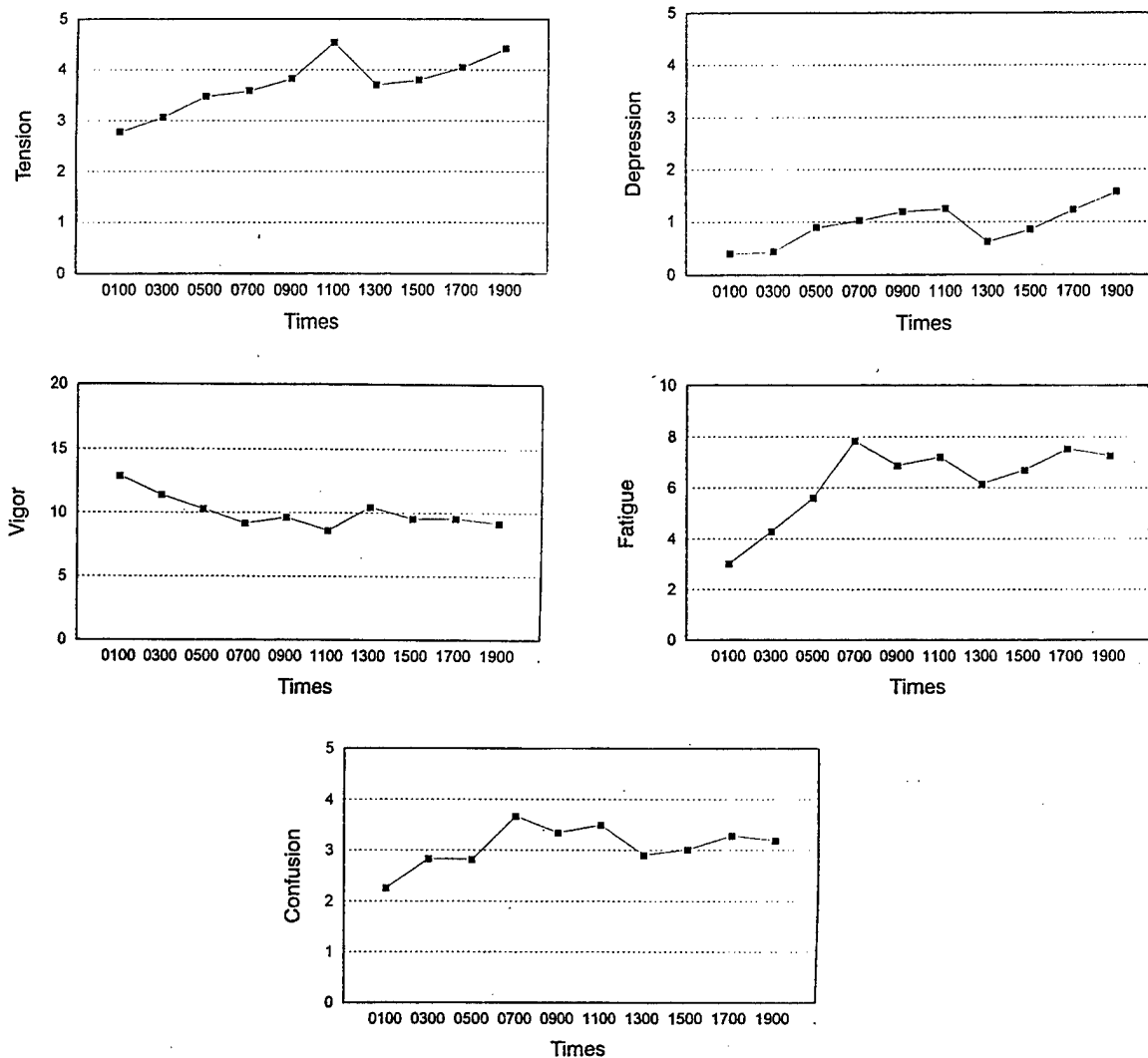


Figure 4. Effects of time of day (with conditions collapsed) on POMS ratings

Energy. The analysis of energy ratings indicated a significant condition-by-time interaction ($F(40,680)=2.81, p<.0001$) and a significant time main effect ($F(20,340)=5.74, p<.0001$). The interaction was because of differences among the three conditions at 2300, 0400, 0500, 0700, and 0800 ($p<.05$), but not elsewhere (see figure 7). Pairwise contrasts at 2300 indicated energy ratings were lower after both Znap and Pnap in comparison to Nonap; however, at all of the remaining times (where there was a significant condition effect), energy ratings after Znap were better than those after Nonap. At 0400, 0700, and 0800, ratings after Pnap also were better than those after Nonap. Znap was significantly better than Pnap only at 0500 ($p<.05$).

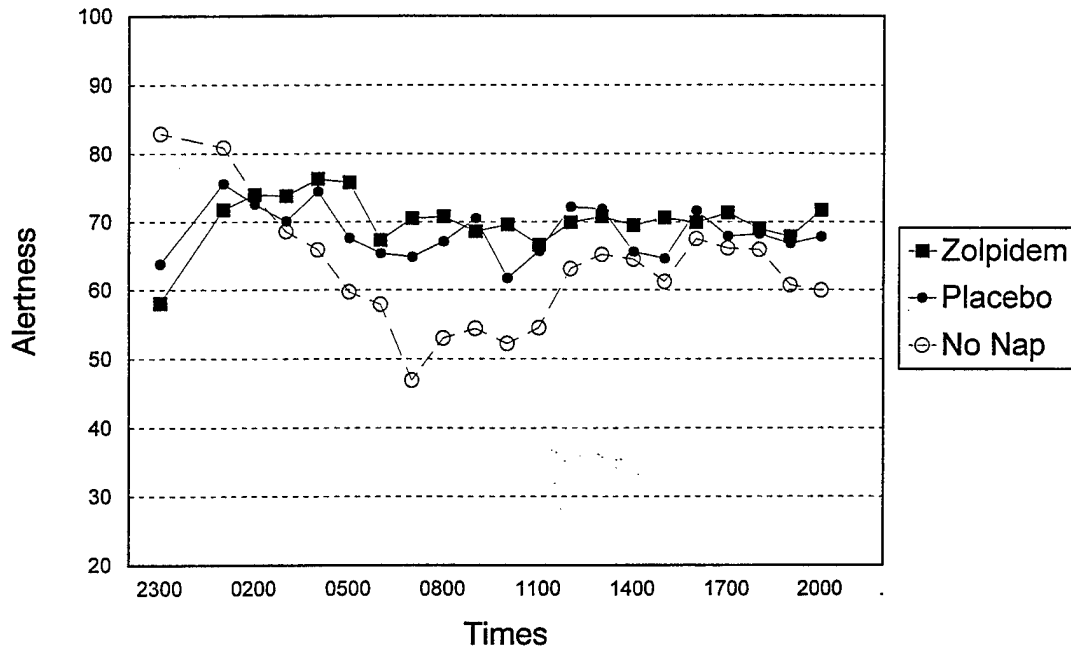


Figure 5. Effects of the three conditions on VAS alertness ratings

The time main effect was attributable to general reductions in energy from early in the morning (0100) until about 1100, after which energy ratings increased from 1100 to 1300, and then dropped until the last session of the day. Specifically, energy ratings were higher at 0100 than at any of the times from 0300 to 1900; they were higher at 0300 than at all of the remaining times except 1300; and they were higher at 0500 than at 0700 or 1100. Energy ratings were lower at 0700 and 0900 than at 1300; and higher at 1300 than at 1500, 1700, and 1900 (see figure 6).

Confidence. The analysis of confidence ratings revealed a condition-by-time interaction ($F(40,680)=2.14$, $p=.0001$) and a time main effect ($F(20,340)=3.10$, $p<.0001$). The interaction was due to a difference among conditions at 2300, but not elsewhere ($p<.05$). Contrasts showed this was attributable to lower confidence ratings after both Znap and Pnap than after Nonap (see figure 8). Examining the interaction in a different way, it was found that there was a difference among the different times only under the Nonap condition, but not after either Znap or Pnap; however, pairwise contrasts were not performed.

The time main effect was similar to the ones reported earlier for energy and alertness. Generally speaking, confidence ratings started out high, dropped until about 1100, recovered slightly, and then dropped again. Pairwise contrasts showed higher confidence ratings at 0100 than at all of the remaining times except 1300; higher ratings at 0300 than at 0700, 0900, 1100, and 1700; and higher ratings at 0500 than at 0700, 0900, and 1100. There were no other significant effects (see figure 6).

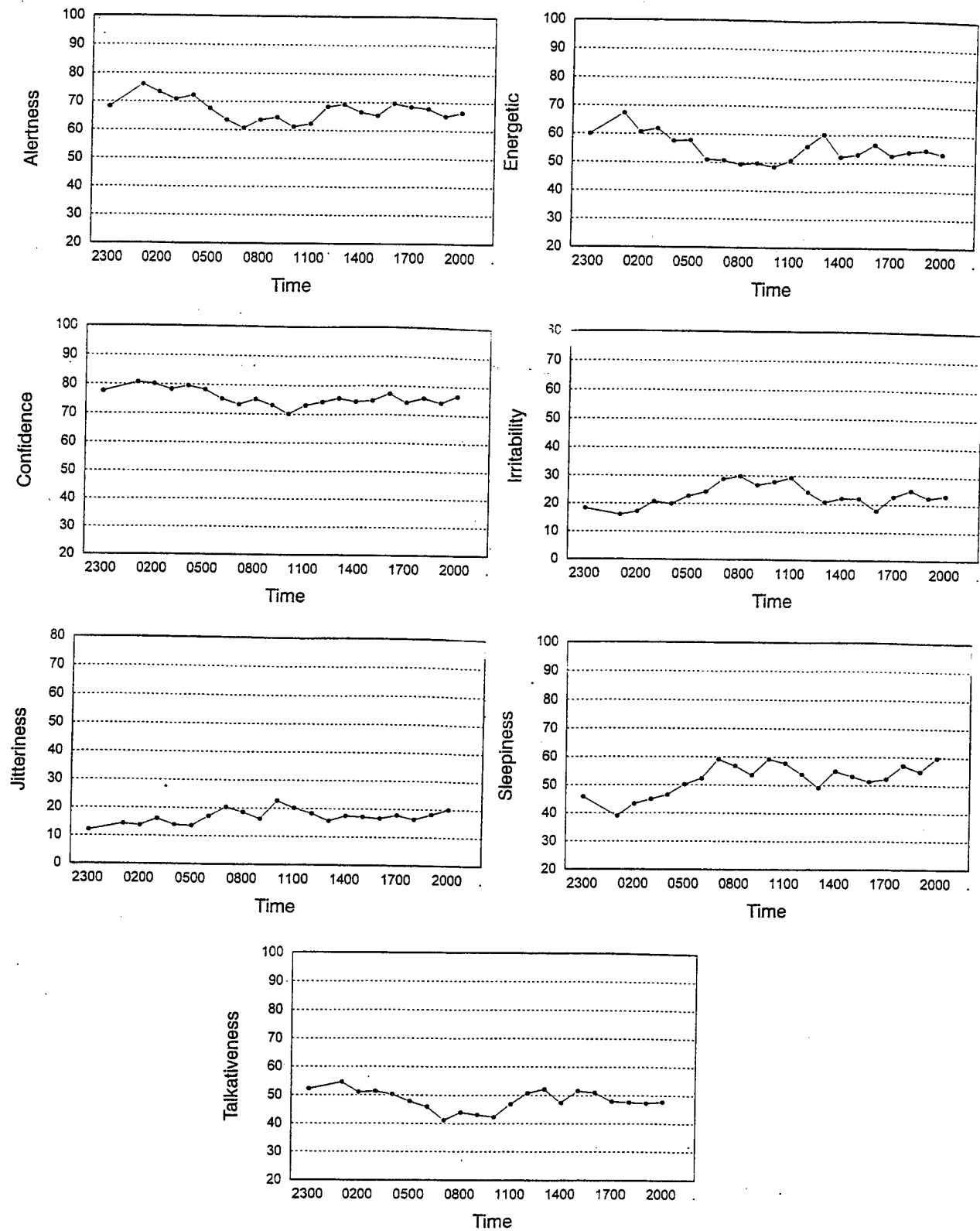


Figure 6. Effects of time of day (with condition collapsed) on VAS ratings

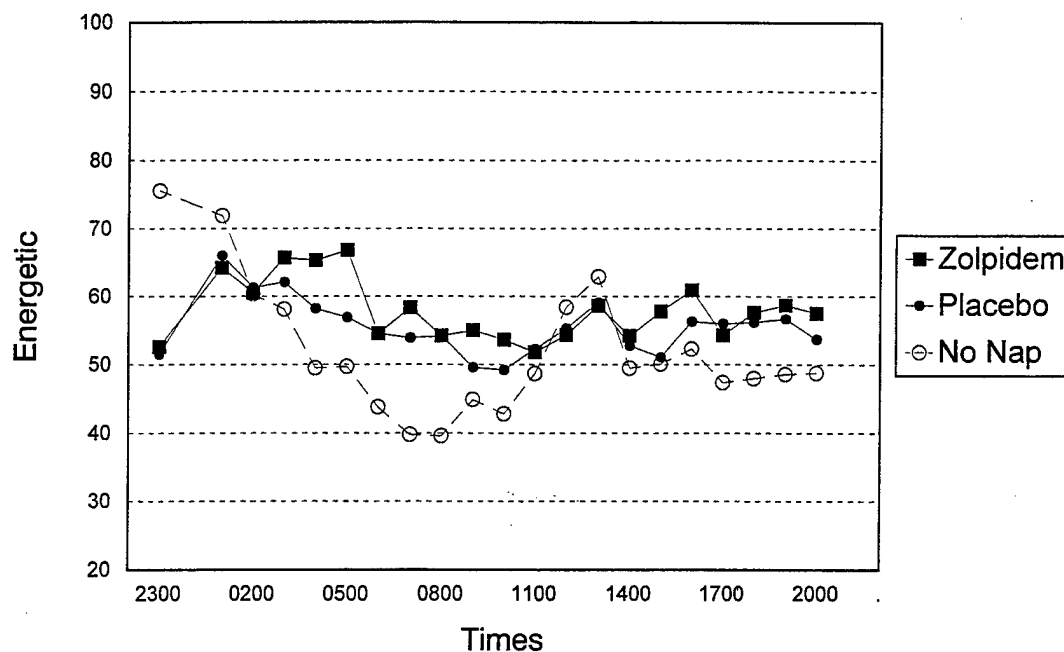


Figure 7. Effects of the three conditions on VAS energy ratings

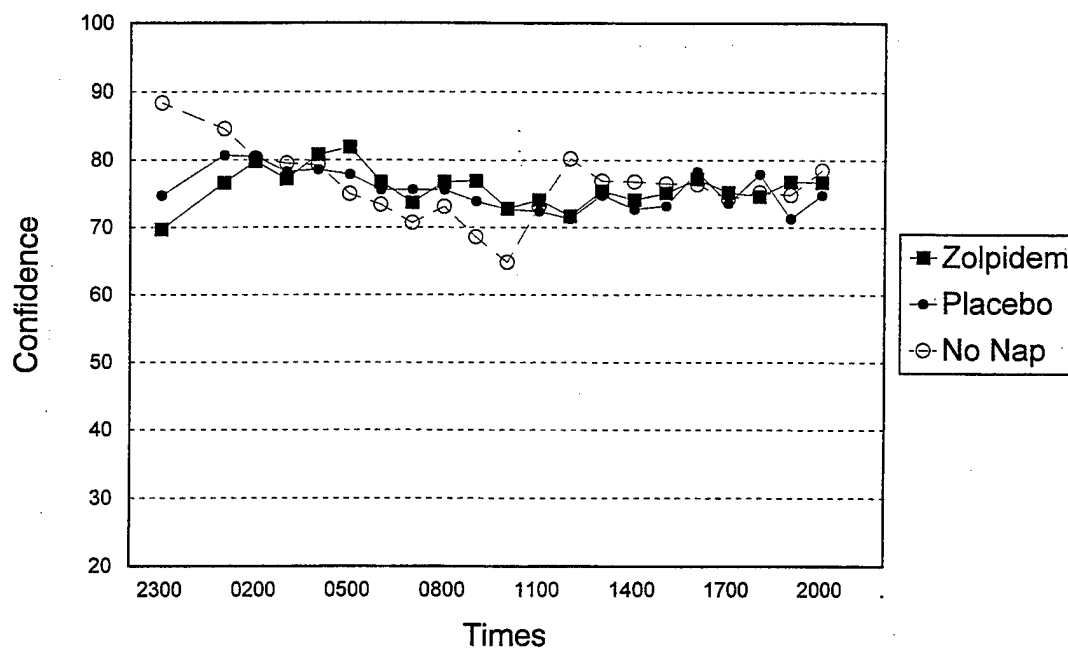


Figure 8. Effects of the three conditions on VAS confidence ratings

Irritability. Analysis of irritability ratings indicated a condition-by-time interaction ($F(40,680)=1.88, p=.0010$), a condition main effect ($F(2,34)=4.10, p=.0254$), and a time main effect ($F(20,340)=3.47, p<.0001$). The interaction was due to differences among the conditions at 2300, 0400, 0500, 0600, 0700, and 0800, but not elsewhere ($p<.05$).

At 2300, subjects were more irritable after Znap and Pnap than after Nonap. At each of the remaining times, subjects were less irritable after Znap than Nonap; and at 0700, they were less irritable after Pnap than Nonap. Comparisons between Znap and Pnap at each time point indicated that Znap was superior to Pnap at 0500, 0600, and 0800. These differences are depicted in figure 9.

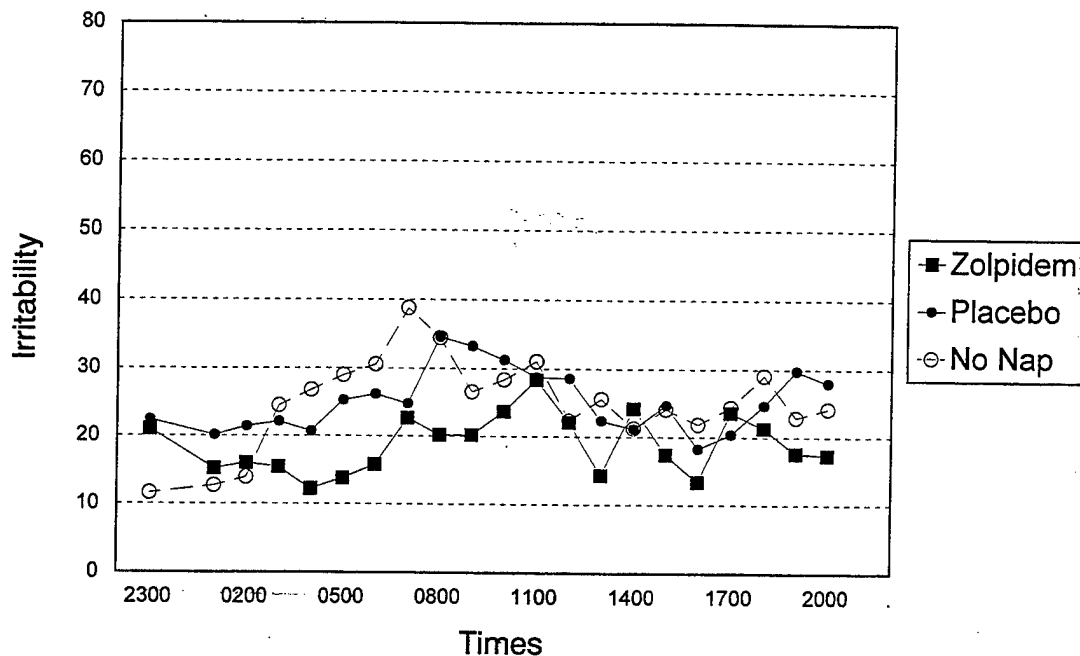


Figure 9. Effects of the three conditions on VAS irritability ratings

The condition main effect showed that overall irritability ratings were lower after Znap than after Pnap or Nonap ($p < .05$). The time main effect revealed that irritability ratings generally were lowest in the early morning, highest toward the middle of the day, and then somewhat lower at the end of the day. Specifically, these ratings were lower at 0100 than at 0500, 0700, 0900, and 1100; lower at 0300 than at 0700 or 1100; lower at 0500 than at 1100. Irritability ratings here higher at 0700 and 0900 than at 1300, and higher at 1100 than at 1500, 1700, or 1900 (see figure 6).

Jitteriness. The ANOVA on jitteriness ratings indicated only a time main effect ($F(20,340)=2.33$, $p=.0012$) with no other main effects or interactions. The time effect was because of lower ratings at 0300 than at 0700; and lower ratings at 0500 than at 0700, 0900, 1100, 1700, and 1900 ($p < .05$). These changes are depicted in figure 6.

Sleepiness. The analysis of sleepiness ratings revealed a condition-by-time interaction ($F(40,680)=3.88$, $p < .0001$), a condition main effect ($F(2,34)=6.63$, $p=.0037$), and a time main effect ($F(20,340)=5.94$, $p < .0001$). The interaction was attributable to the fact that there were differences among the three conditions at 2300, 0400, 0500,

0600, 0700, 0800, 1400, 1500, 1700, 1800, 1900, and 2000, but not elsewhere (see figure 10). Contrasts at 2300 showed sleepiness was higher after Znap and Pnap than after Nonap. However, at all of the remaining times except 1400, sleepiness was lower after Znap than after Nonap. At all of the times except 1800 and 1900, sleepiness was lower after Pnap than Nonap. Ratings of sleepiness after Znap were lower than those after Pnap only at 2000.

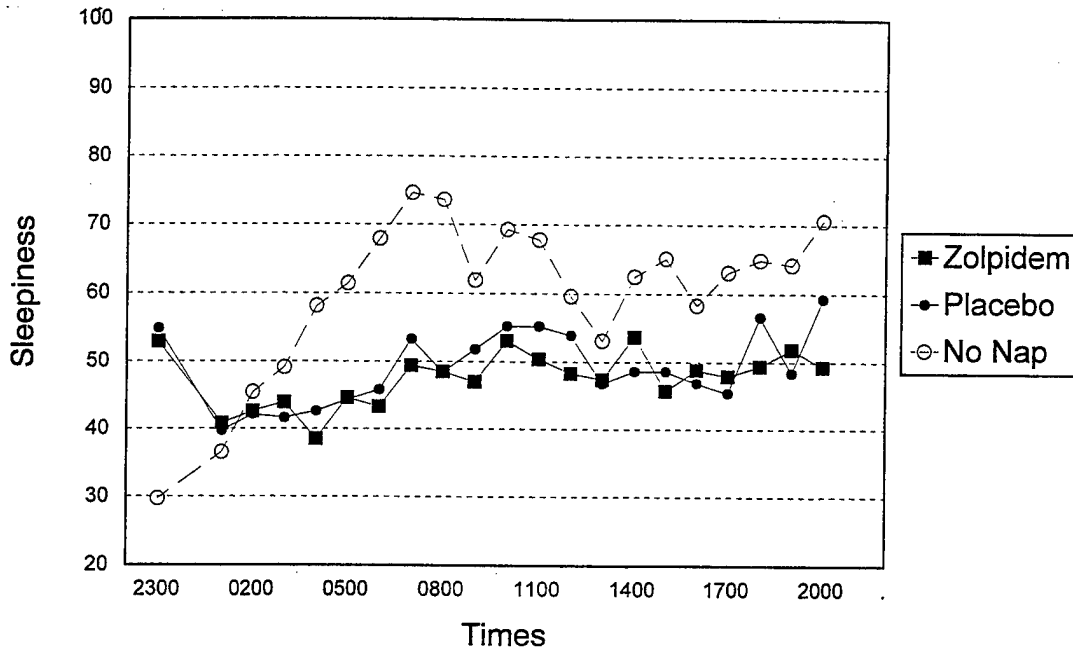


Figure 10. Effects of the three conditions on VAS sleepiness ratings

The condition main effect was due to lower sleepiness ratings after both napping conditions than after the Nonap condition (the means were: Znap-47.5, Pnap-49.0, and Nonap-59.8). The time main effect was due to an increase in sleepiness from 0100 until 1100 followed by a slight reduction and then a final increase. Pairwise contrasts showed lower sleepiness ratings at 0100 than at all of the remaining times; lower ratings at 0300 than at 0500, 0700, 0900, 1100, and 1900; lower ratings at 0500 than at 0700 and 1100; and lower ratings at 0900 than at 1100. Conversely, sleepiness was higher at 0700, 0900, and 1100 than at 1300; and it was higher at 1100 than at 1500 or 1700 ($p < .05$). These differences are shown in figure 6.

Talkativeness. The ANOVA on ratings of talkativeness indicated a significant condition-by-time interaction ($F(40,680)=1.74$, $p=.0037$), a significant condition main effect ($F(2,34)=3.39$, $p=.0455$), and a significant time main effect ($F(20,340)=3.09$, $p<.0001$). Analysis of simple effects indicated the interaction was because of differences among the conditions at 2300, 0500, and 0700 ($p<.05$). The effect at 2300 was due to reduced ratings of talkativeness after both Znap and Pnap than after the

Nonap condition. However, in the remaining two sessions, ratings of talkativeness were higher after Znap than after Nonap; and at 0500, ratings were higher after Pnap than after Nonap as well (see figure 11).

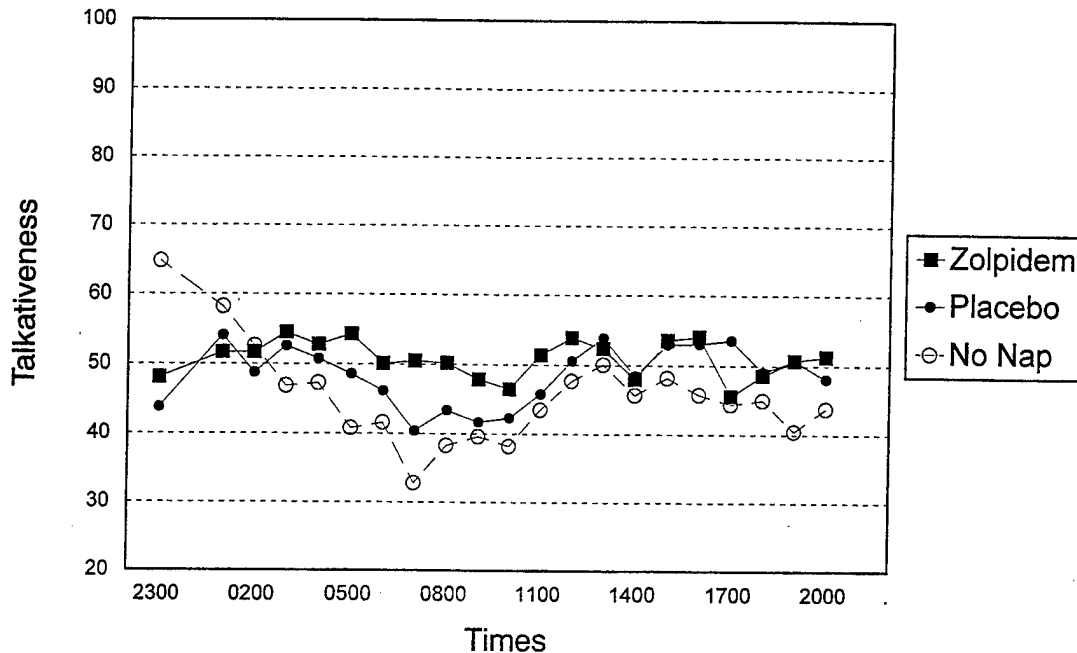


Figure 11. Effects of the three conditions on VAS talkativeness ratings

The condition main effect was because of more talkativeness after Znap than Nonap ($p < .05$). None of the other comparisons were significant. The time main effect was due to higher ratings of talkativeness at 0100 than at 0300, 0500, 0700, 0900, 1100, and 1700; higher ratings at 0300 than at 0500, 0700, or 0900; and a higher rating at 0500 than at 0700. Ratings were lower at 0700 and at 0900 than at 1300 and 1500; and lower at 1100 than at 1300 ($p < .05$). These differences are shown in figure 6.

RTSW

The data from the RTSW were analyzed with a 3 by 10 repeated measures ANOVA for condition (Znap, Pnap, and Nonap) and time (0210, 0410, 0610, 0810, 1010, 1210, 1410, 1610, 1810, and 2010). The ANOVA revealed a condition-by-time interaction ($F(14.5, 246.2) = 2.43$, $p = .0029$), a condition main effect ($F(2, 34) = 32.38$, $p < .0001$), and a time main effect ($F(6.4, 108.3) = 19.85$, $p < .0001$). The interaction was because differences among the conditions were larger during the first half than the second half of the day (figure 12). Comparisons among the three conditions at each testing time indicated that subjects were better able to remain awake after Znap than after Nonap throughout the testing day (100 percent of the time). Pnap was better than Nonap at every test time with the exception of 1410 and 1610 (80 percent of the time). Znap was

significantly better than Pnap at 0410, 1010, 1410, 1810, and 2010 (or about 50 percent of the time).

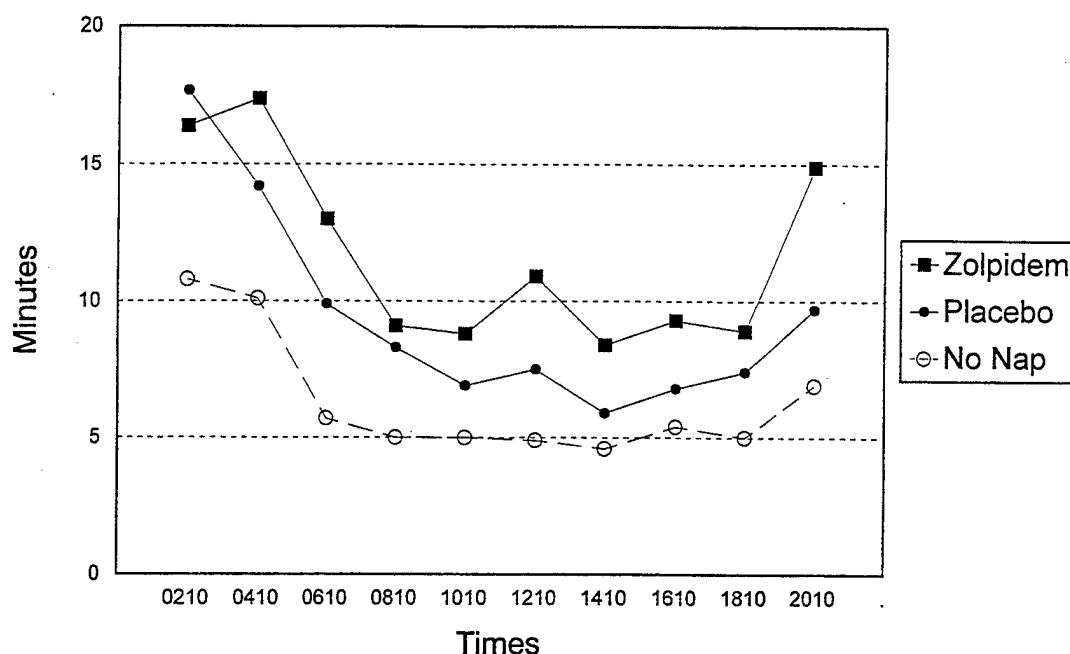


Figure 12. Effects of the three conditions on RTSW sleep latency

The condition main effect showed that overall ability to sustain wakefulness was better after Znap than after the other interventions, and better after Pnap than after Nonap ($p < .05$). The mean number of minutes awake after each intervention were: Znap-11.7, Pnap-9.4, and Nonap-6.3.

The time main effect was because of a general decline in subjects' abilities to remain awake as the day progressed (with the exception of a slight improvement in alertness at the last time of the day). As can be seen in figure 13, sleep latencies were longer at 0210 and 0410 than at any of the remaining times; longer at 0610 than at 0810, 1010, 1210, 1410, and 1610; and longer at 2010 than at all the other times except 0610 ($p < .05$).

Cognitive evaluations

MATB

Scores on several aspects of each of the subtests of the MATB were analyzed separately with 3 by 5 repeated measures ANOVAs for condition (Znap, Pnap, and Nonap) and time (0110, 0510, 0910, 1310, and 1710). Significant effects were followed up with analysis of simple effects and/or pairwise contrasts.

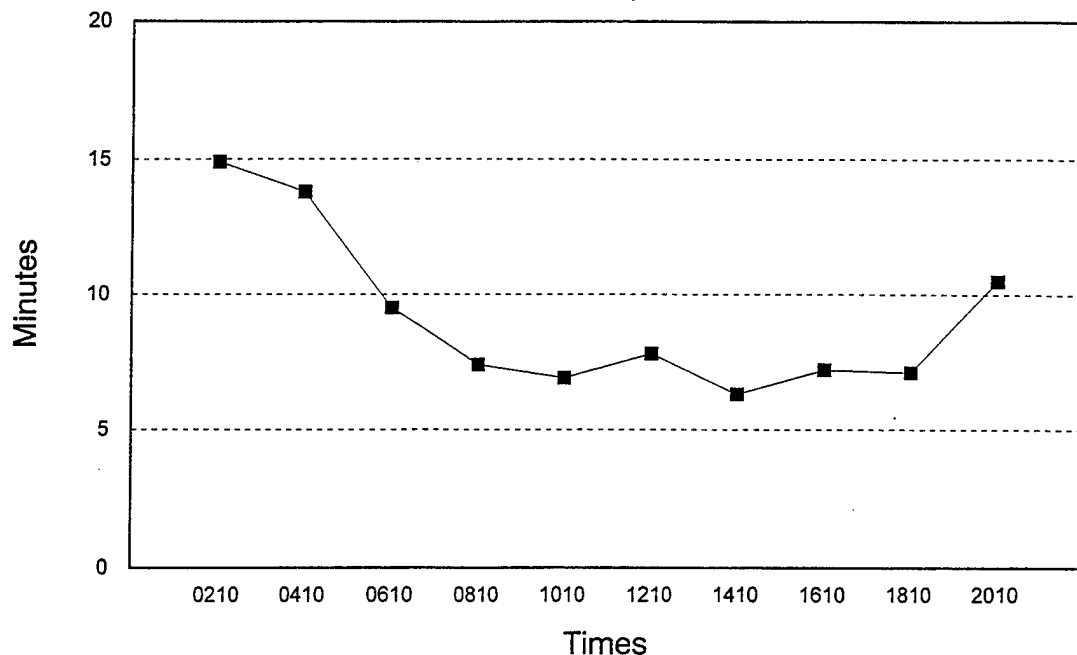


Figure 13. Effect of time of day (with conditions collapsed) on RTSW sleep latency

Resource management. Data for this task consisted of the mean deviation of units of “fuel” in tanks A and B from the target of 2500, the mean number of “fuel” units in tank A, and the mean number of “fuel” units in tank B. The ANOVA on these data indicated there were no significant main effects or interactions.

Communications. Data for the communications task consisted of the mean reaction time (RT) for correct responses, the standard deviation of reaction times (SDRT) for correct responses, and the number of time-out errors. The ANOVA on these data indicated that there was a significant condition-by-time interaction only on the mean RT for correct responses ($F(8,136)=2.49$, $p=.0148$). Analysis of simple effects showed this was due primarily to differences among the three conditions at 1710, but not elsewhere. Contrasts at 1710 showed that RT was shorter after both Znap and Nonap than after Pnap (see figure 14).

There were time main effects on the mean RT for correct responses ($F(4,68)=5.21$, $p=.0010$), the SDRT for correct responses ($F(4,68)=2.93$, $p=.0271$), and the number of time out errors ($F(4,68)=3.06$, $p=.0221$). Mean RT for correct responses was greater at 0910 than at 0110 or 1710, and greater at 0510 than at 1710 ($p<.05$). SDRT for correct responses was greater at 0110 than at 0510, 0910, and 1310, and greater at 0510 than at 0710 ($p<.05$). Time out errors were more numerous at 0910 and 1310 than at 0110 or 1710 ($p<.05$). All of these effects are depicted in figure 15.

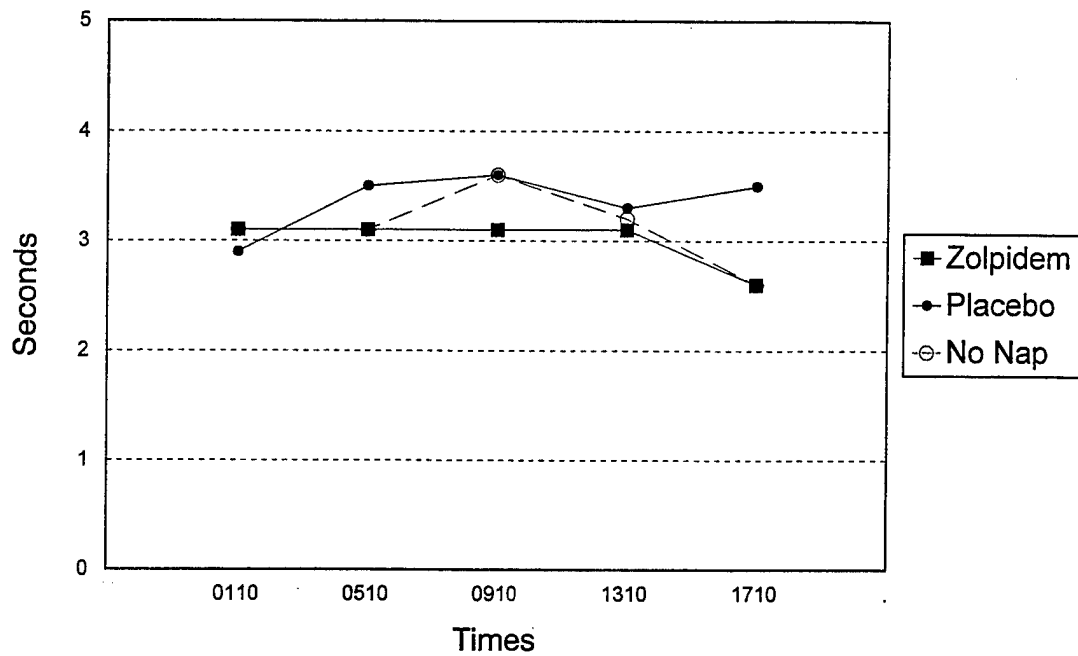


Figure 14. Effects of the three conditions on RT in the MATB communications task

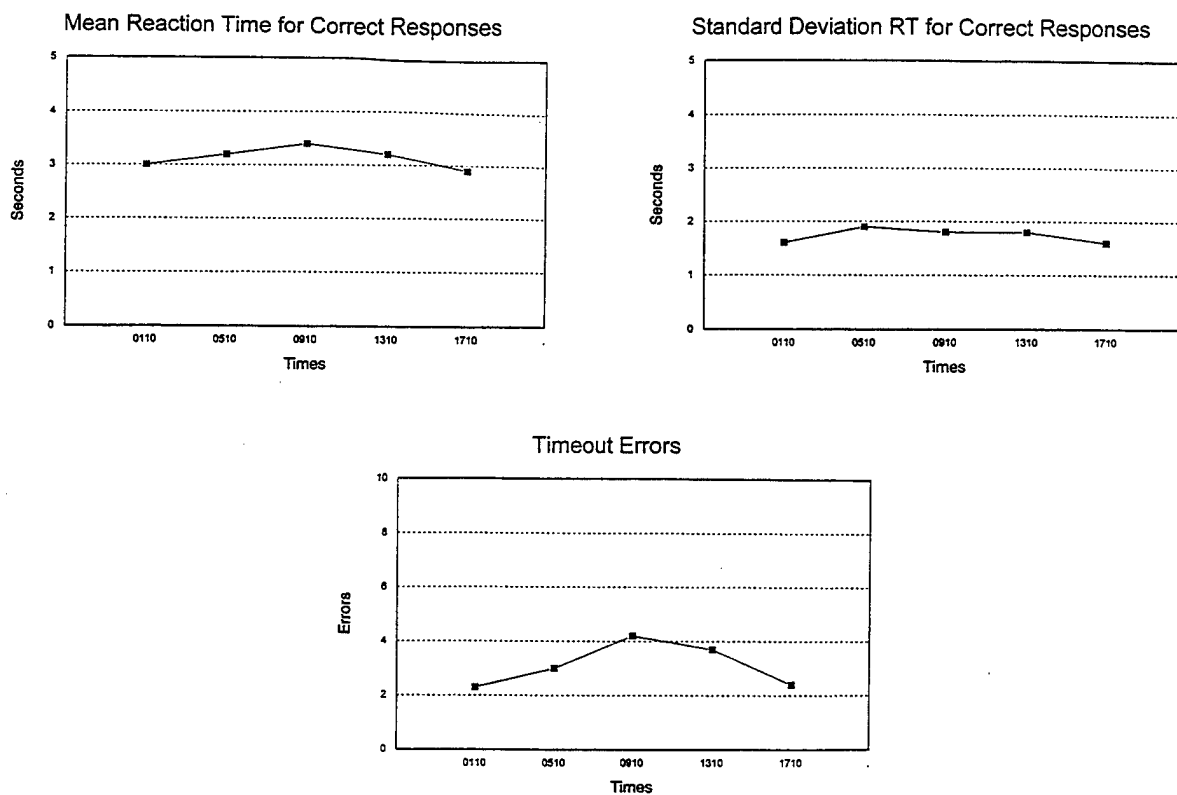


Figure 15. Effects of time of day on mean RT, SDRT, and time-out errors in the MATB communications task

Systems monitoring. Data for this task consisted of the RT for responding to lights, the RT for responding to dial deviations, the SDRT for lights, the SDRT for dials, time-out errors for lights, and time-out errors for dials. The ANOVA on these data indicated significant condition-by-time interactions on the mean RT for lights ($F(8,136)=2.97$, $p=.0043$), the mean RT for dials ($F(8,136)=4.39$, $p=.0001$), and the SDRT for lights ($F(8,136)=3.09$, $p=.0031$). In each of these cases, analysis of simple effects revealed differences among the three conditions at 0910 but not at the other testing times ($p<.05$). Contrasts at 0910 showed that the RT for lights and the RT for dials were faster after Znap than after Nonap ($p<.05$). The mean RT for dials was shorter after Pnap than after Nonap. In addition, the mean RT for lights was shorter after Znap than after Pnap ($p<.05$). With regard to the SDRT for lights, it was smaller after Znap than after either Pnap or Nonap, while the difference between Pnap and Nonap was not significant. These effects are depicted in figure 16.

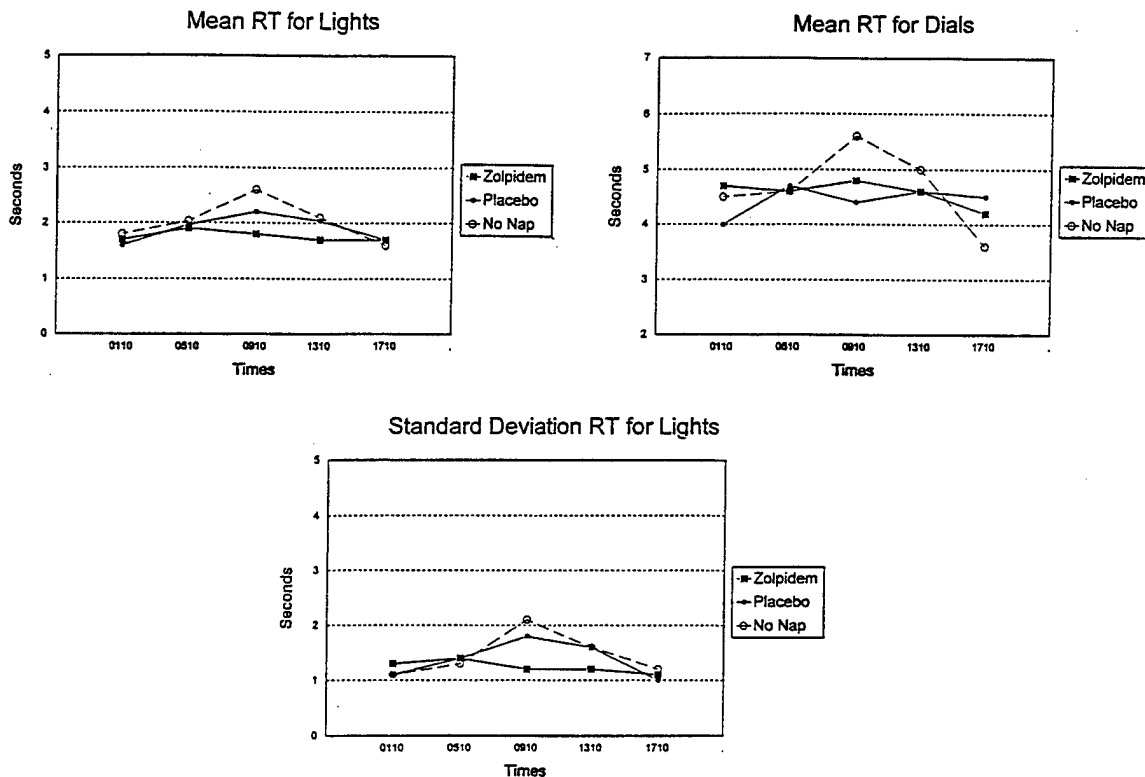


Figure 16. Effects of the three conditions on mean RT for lights, mean RT for dials, and SDRT for lights in the MATB systems monitoring task

There was a condition main effect for RT for lights ($F(2,34)=4.92$, $p=.0132$) due to an overall reduction in response time after Znap in comparison to Nonap. The means were: Znap-1.77, Pnap-1.92, and Nonap-1.99.

There were time main effects on the mean RT for lights ($F(4,68)=7.49$, $P<.0001$), the mean RT for dials ($F(4,68)=5.70$, $p=.0005$), the SDRT for lights ($F(4,68)=7.14$, $p=.0001$), the SDRT for dials ($F(4,68)=2.67$, $p=.0391$), the number of time out errors for lights ($F(4,68)=3.22$, $p=.0176$), and the number of time out errors for dials ($F(4,68)=3.65$, $p=.0094$). In most cases, performance tended to be poorer in the late morning than at the beginning or end of the day. The mean RT for lights was faster at 0110 than at 0510, 0910 or 1310; faster at 0510 than 0910; slower at 0910 than at 1310 or 1710; and slower at 1310 than at 1710 ($p<.05$). The mean RT for dials was slower at 0510, 0910, and 1310 than it was at 1710 and faster at 0110 than at 0910 or 1310 ($p<.05$). The SDRT for lights was smaller at 0110, 0510, 1310, and 1710 than it was at 0910; and larger at 1310 than at 1710 ($p<.05$). The SDRT for dials was smaller at 1710 than at 0910 and 1310 ($p<.05$). The number of time out errors both for lights and dials was smaller at 0110 than at 0910 and 1310; and slower at 0910 and 1310 than it was at 1710 ($p<.05$). All of these time main effects are depicted in figure 17.

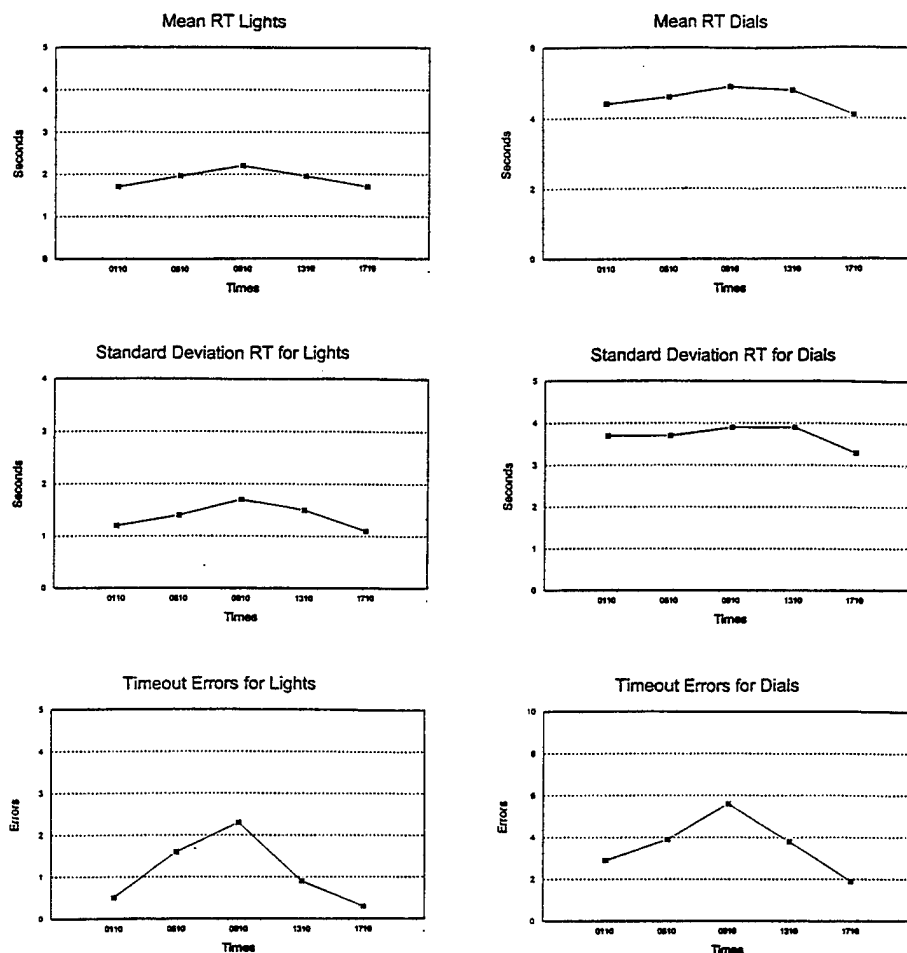


Figure 17. Effects of time of day on performance of the MATB systems monitoring task

Tracking. Data for the tracking task consisted of root mean square (RMS) deviations of the tracking target from the center of the upper right-hand quadrant of the computer screen. On these data there was a condition-by-time interaction ($F(7.24, 123.01)=2.24$, $p=.0336$) and a time main effect ($F(2.68, 45.64)=3.73$, $p=.0210$). The interaction occurred because there were differences among the conditions at 0910 ($p<.05$), but not at other testing times. Contrasts for the effect at 0910 indicated that tracking errors were smaller after Znap than after Pnap or Nonap (see figure 18).

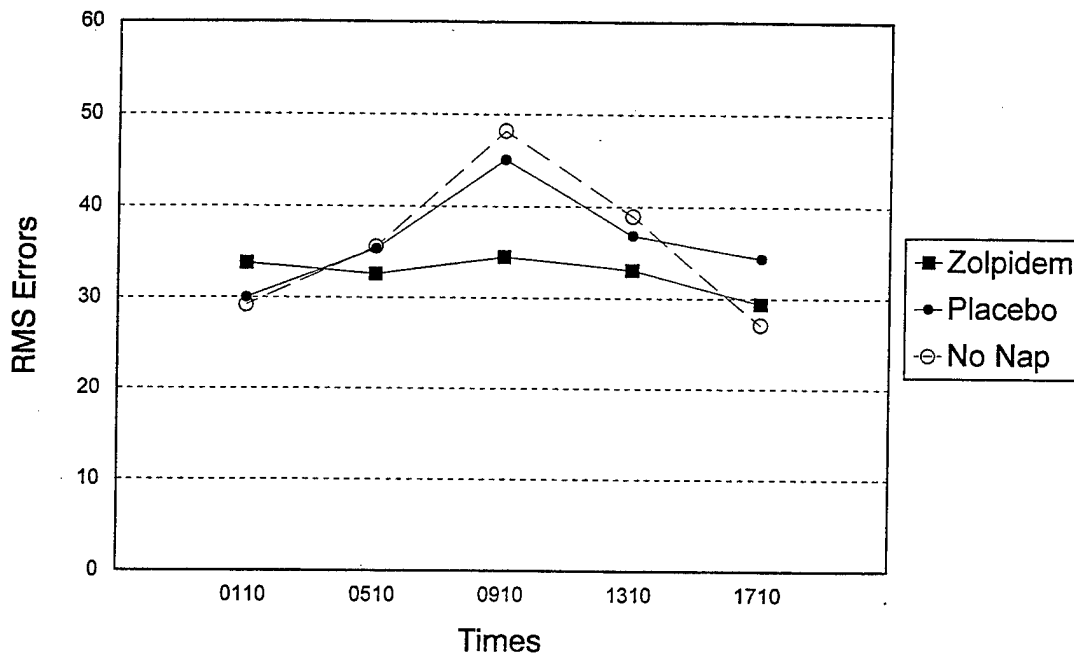


Figure 18. Effects of the three conditions on MATB tracking errors

The main effect on the time factor was due to an increase in errors from 0110 to 0910 followed by a decrease in errors from 0910 to 1710 (see figure 19). Contrasts revealed significantly larger tracking deviations at 0910 than at 0110 and at 1710 ($p<.05$). In addition, tracking errors were larger at 1310 than at 1710 ($p<.05$) and tended to be larger at 1310 than at 0110 ($p=.06$).

SYNWORK

Composite scores representing overall performance on each of the SYNWORK tasks (Sternberg memory, arithmetic, visual monitoring, and auditory monitoring) were analyzed separately with a 3 by 5 repeated measures ANOVA for condition (Znap, Pnap, and Nonap) and time (0305, 0705, 1105, 1505, and 1905). The ANOVAs indicated there were significant condition-by-time effects on performance of the Sternberg task ($F(8, 136)=2.47$, $p=.0156$) and the arithmetic task ($F(8, 136)=2.26$, $p=.0269$). Analysis of simple effects on the Sternberg task revealed a difference among

conditions at 1105 ($p < .05$), but not elsewhere. Contrasts showed this was because performance after Znap was better than performance after Pnap ($p < .05$), while neither of these differed from Nonap (see figure 20). Analysis of simple effects on the arithmetic task indicated a tendency toward a difference among conditions at 0705 ($p = .08$), but not at the other testing times. Contrasts showed the effect at 0705 tended to result from better performance after both Znap and Pnap than after Nonap ($p = .07$), as depicted in figure 20.

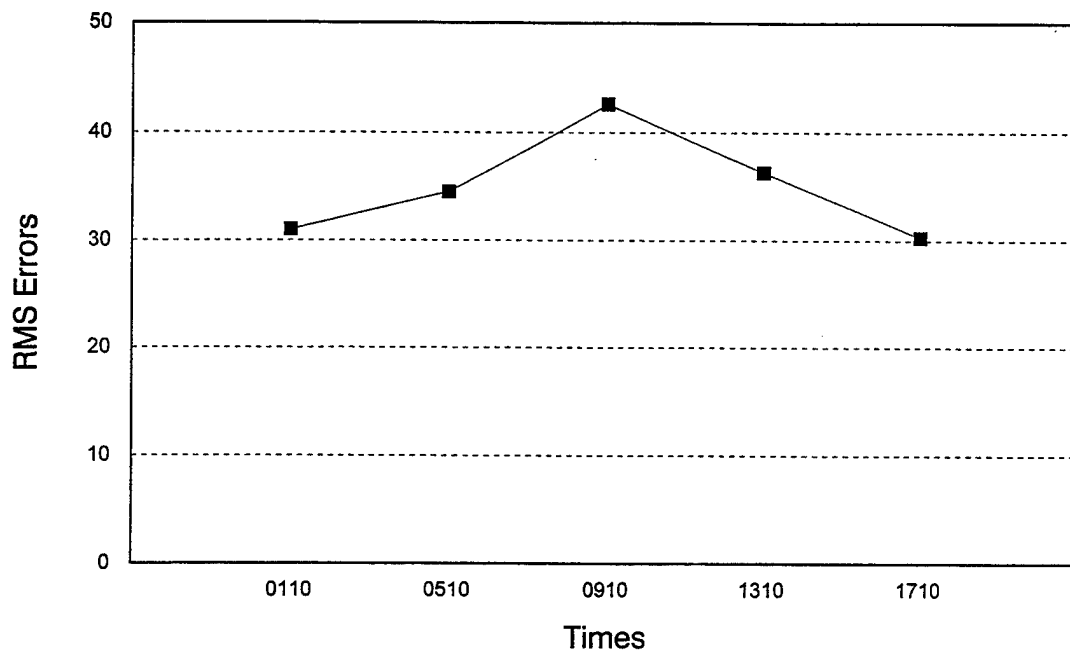


Figure 19. Effects of time of day (with conditions collapsed) on MATB tracking errors

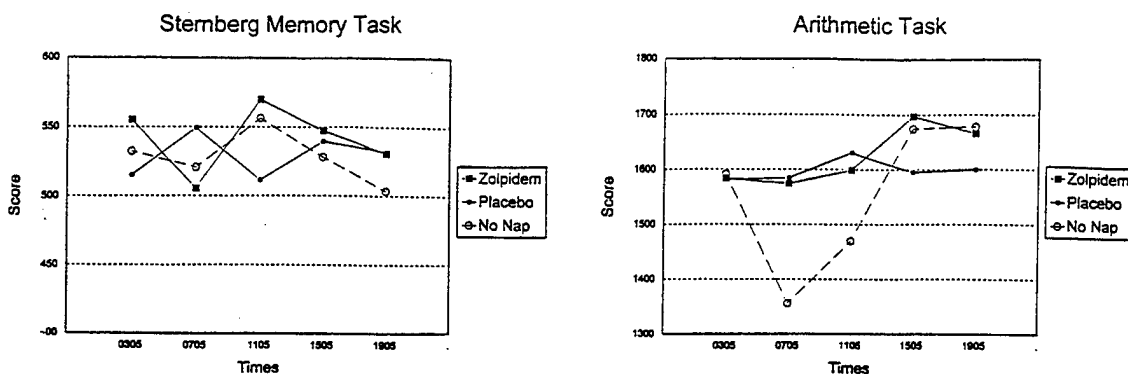


Figure 20. Effects of the three conditions on SYNWORK scores

There were time main effects on both the arithmetic task ($F(4,68)=3.12$, $p=.0204$) and the auditory monitoring task ($F(4,68)=4.21$, $p=.0042$). Contrasts indicated the time effect on arithmetic resulted from better scores at 1905 than at 0705 or 0305, and better scores at 1505 than at 0705 ($p < .05$). The time effect on auditory monitoring resulted

from better scores at 1505 than at 1905, and poorer scores at 0705 than at 0305, 1105, or 1505 ($p < .05$). These effects are depicted in figure 21.

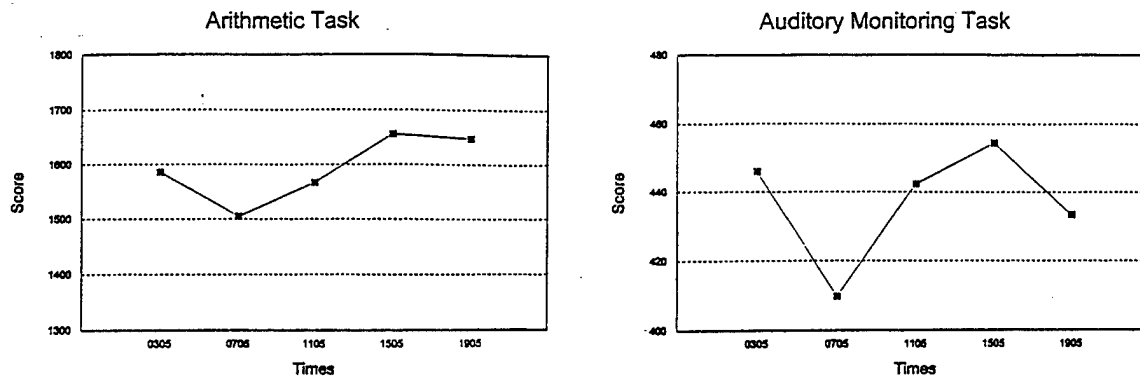


Figure 21. Effects of time of day on SYNWORK arithmetic and auditory monitoring scores

There was one main effect on the condition factor, and this occurred on the scores from the visual monitoring task ($F(1.7, 28.8) = 4.18$, $p = .0311$). Contrasts showed that the scores after both Znap and Pnap were higher than those after Nonap (see figure 22). Note that although there appears to be an interaction in these data, the F value was not significant ($p > .10$).

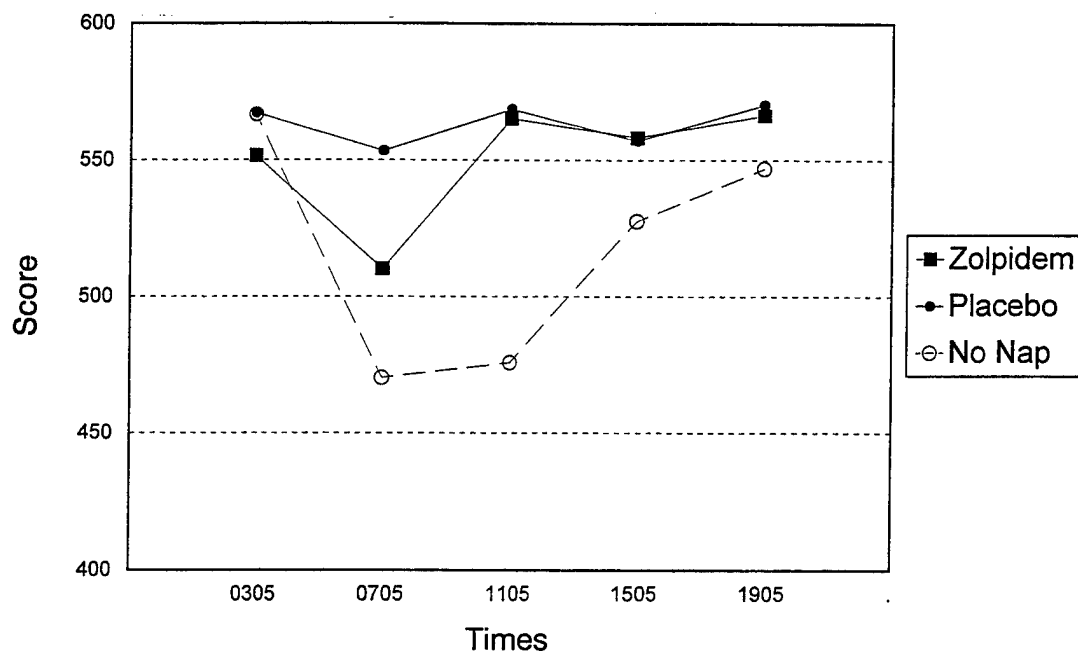


Figure 22. Effects of the three conditions on SYNWORK visual monitoring scores

Waking EEG evaluations

For the resting EEG, each power band (beta, alpha, theta, and delta) from seven electrode sites (Fz, Cz, C3, C4, Pz, O1, and O2) were analyzed separately with 3 by 5 by 2 repeated measures ANOVAs for condition (Znap, Pnap, and Nonap), time (0230, 0630, 1030, 1430, and 1830), and eyes (eyes open and eyes closed).

Delta

The ANOVA on delta activity indicated a condition-by-eyes effect at Cz ($F(2,34)=3.40$, $p=.0453$) which was due to a tendency toward increased delta activity after Nonap in comparison to either Znap or Pnap under eyes closed (see figure 23). A condition-by-time effect at Cz ($F(8,136)=2.02$, $p=.0480$) was attributable to differences among the conditions at 1830 ($p<.05$), but not at other times. As shown in figure 24, there was more delta activity after Nonap than after Pnap ($p<.05$), and there was a similar tendency between Nonap and Znap ($p=.08$) at 1830 (the apparent difference at 1030 was not significant). Examined in another way, there was a tendency toward differences in delta at the various testing times after Nonap ($p=.08$), but not after Znap or Pnap. After Nonap, delta tended to increase at 1030, 1430, and 1830 in comparison to the two earlier test times.

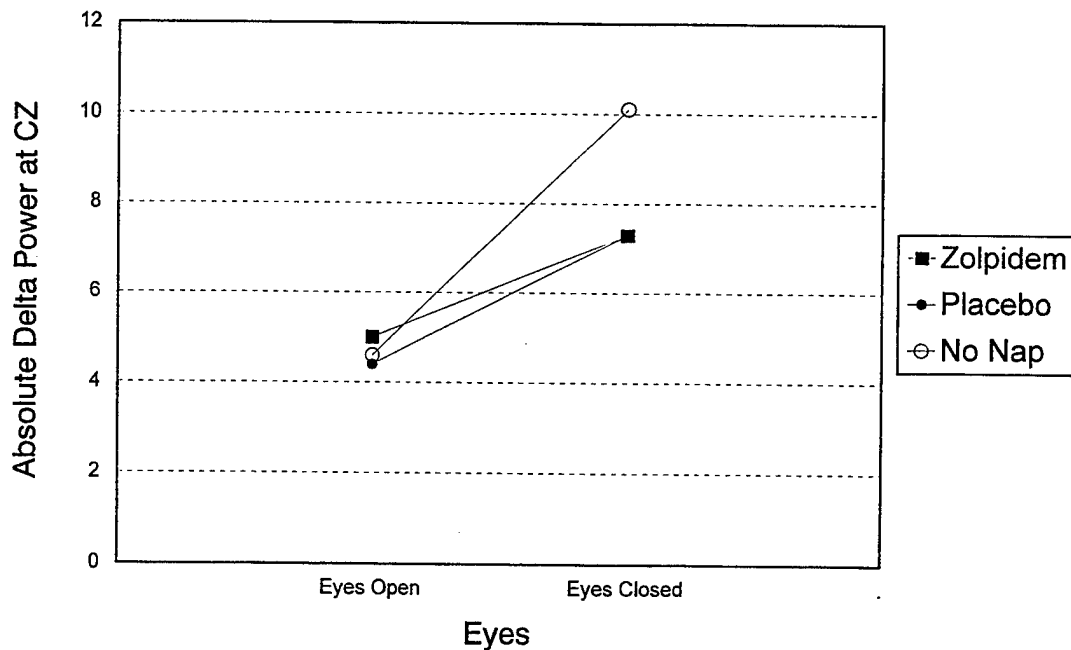


Figure 23. Effects of condition and eyes-open/eyes-closed on delta activity at Cz

There were main effects on the eyes factor at Fz ($F(1,17)=34.95$, $p<.0001$), Cz ($F(1,17)=34.90$, $p<.0001$), C3 ($F(1,17)=49.44$, $p<.0001$), C4 ($F(1,17)=49.27$, $p<.0001$),

Pz ($F(1,17)=36.41$, $p<.0001$), O1 ($F(1,17)=17.89$, $p=.0006$), and O2 ($F(1,17)=21.63$, $p=.0002$). In each case, there was more delta activity with eyes closed than with eyes open. There also was a main effect on the time factor at Fz ($F(4,68)=2.95$, $p=.0261$) which was due to lower delta power at 0230 than at 1030, 1430, or 1830 ($p<.05$). This time main effect is depicted in figure 25.

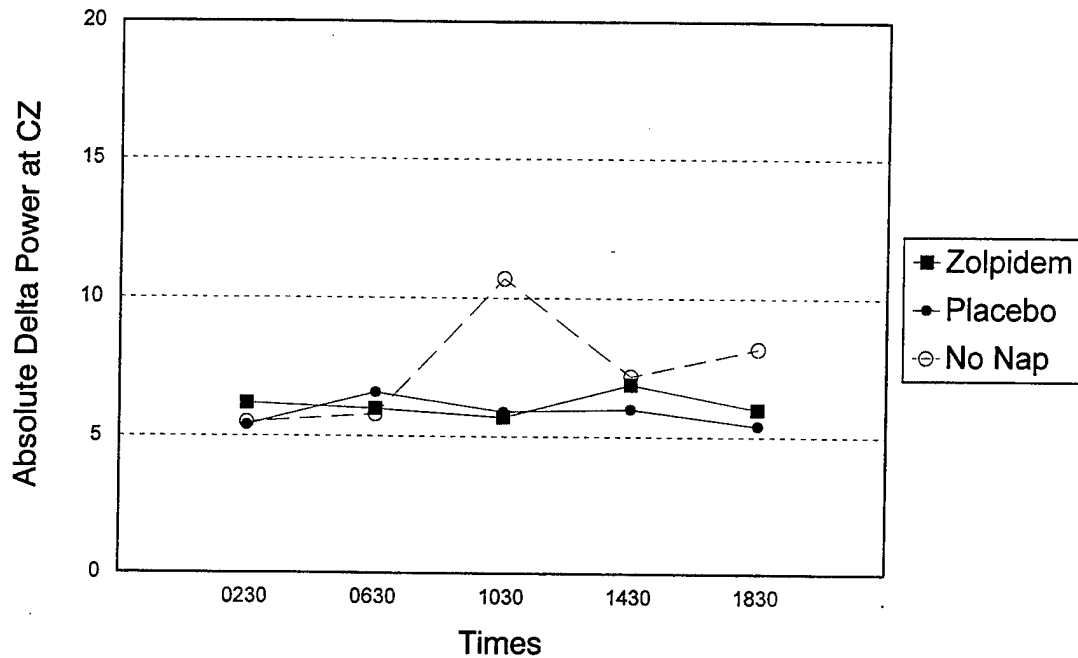


Figure 24. Effects of condition and time of day on delta activity at Cz

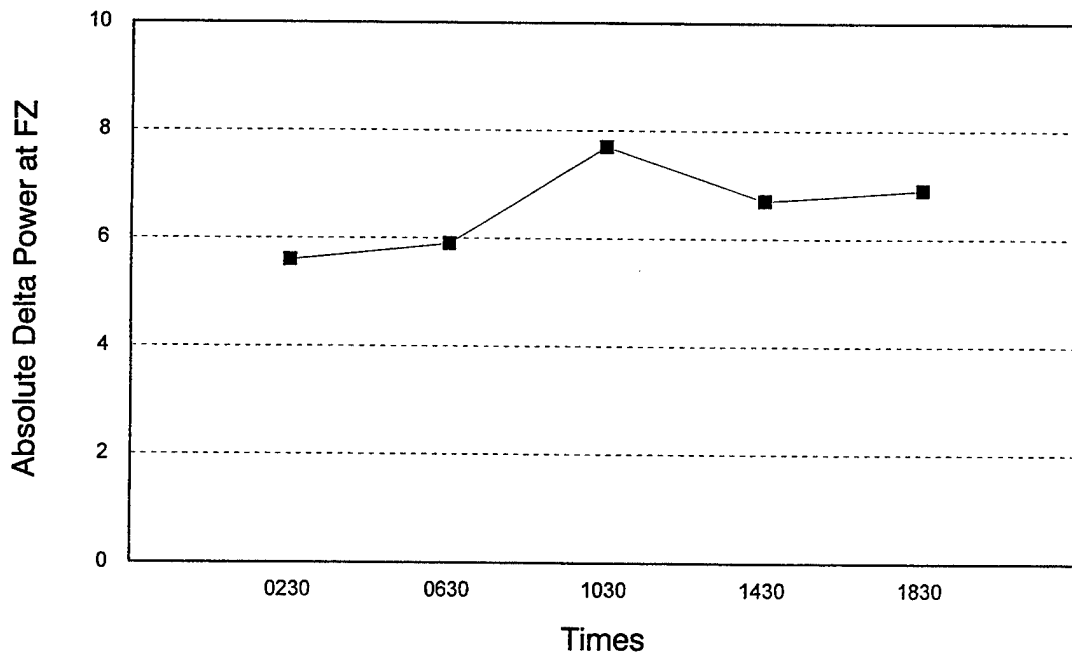


Figure 25. Effect of time of day on delta activity at Fz

Theta

The ANOVA on theta activity showed there were time-by-eyes interactions at Fz ($F(4,68)=2.60$, $p=.0434$), Cz ($F(4,68)=2.80$, $p=.0328$), and C4 ($F(4,68)=2.79$, $p=.0332$). Analysis of simple effects indicated there were differences between the amount of theta recorded at each of these electrodes under eyes open and eyes closed at every testing time ($p<.05$). However, as can be seen in figure 26, the differences (between eyes open and eyes closed) were smaller at 0230 than at any of the later times.

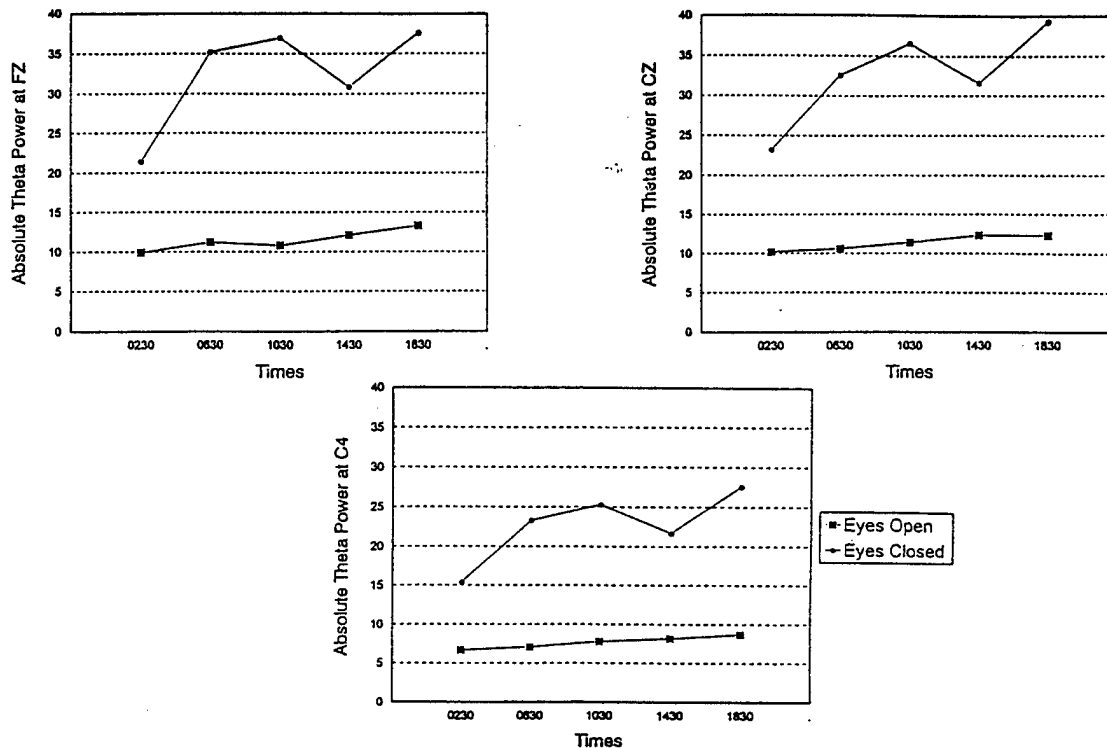


Figure 26. Effects of time of day and eye closure on theta activity at Fz, Cz, and C4

There were several main effects on both the time factor and the eyes factor. There were time main effects at Fz ($F(4,68)=4.07$, $p=.0051$), Cz ($F(4,68)=3.88$, $p=.0067$), C3 ($F(4,68)=3.06$, $p=.0221$), C4 ($F(4,68)=4.35$, $p=.0034$), and Pz ($F(4,68)=2.59$, $p=.0444$). In most cases, these effects were due to increases in theta activity from 0230 to all of the remaining testing times ($p<.05$). At C3 and Pz, the 0230-0630 comparison was not significant, but the remaining comparisons were. All of these time effects are depicted in figure 27. There were eyes main effects at Fz ($F(1,17)=20.77$, $p=.0003$), Cz ($F(1,17)=41.60$, $p<.0001$), C3 ($F(1,17)=39.65$, $p<.0001$), C4 ($F(1,17)=36.61$, $p<.0001$), Pz ($F(1,17)=33.51$, $p<.0001$), O1 ($F(1,17)=20.49$, $p=.0003$), and O2 ($F(1,17)=17.88$, $p=.0006$). All of these were attributable to greater theta activity under eyes closed than under eyes open.

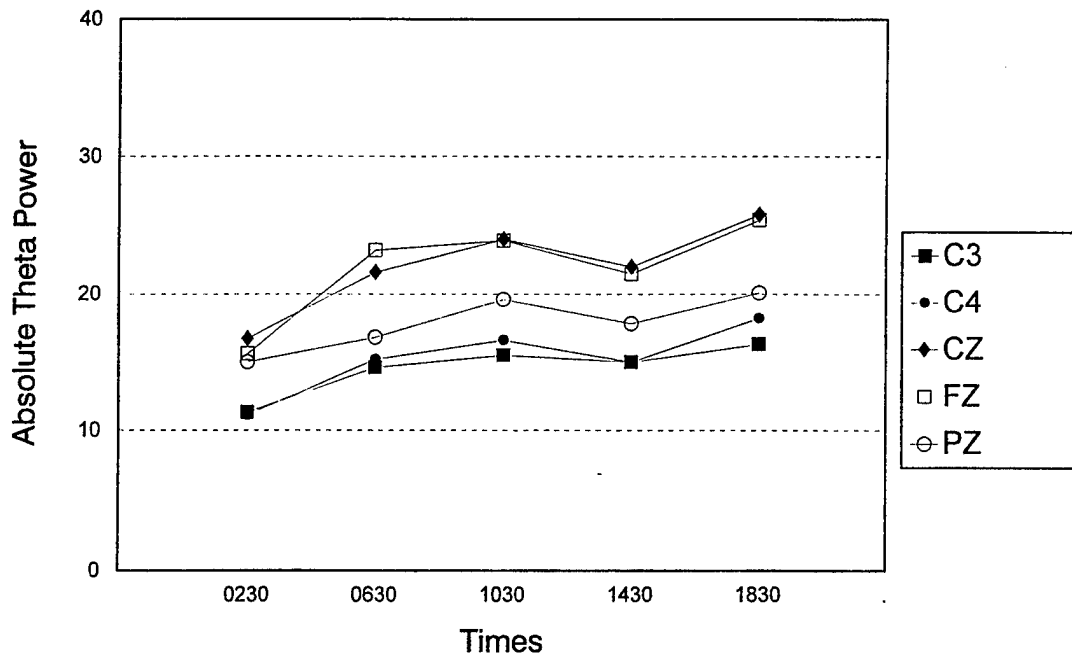


Figure 27. Effect of time of day on theta activity at Fz, Cz, C3, C4, and Pz

Alpha

The ANOVA on alpha activity revealed a three-way interaction among condition, time, and eyes at O1 ($F(8,136)=2.78, p=.0070$). Analysis of simple effects indicated there was a condition-by-time interaction at eyes closed but not at eyes open, and subsequent analyses revealed a difference in the amount of alpha recorded (with eyes closed) at the various times after Nonap, but not after either Pnap or Znap ($p<.05$). This effect was attributable to substantially more alpha at 0230 than at 0630, 1030, or 1830 after Nonap, whereas only a slight decline occurred in the other two conditions (see figure 28).

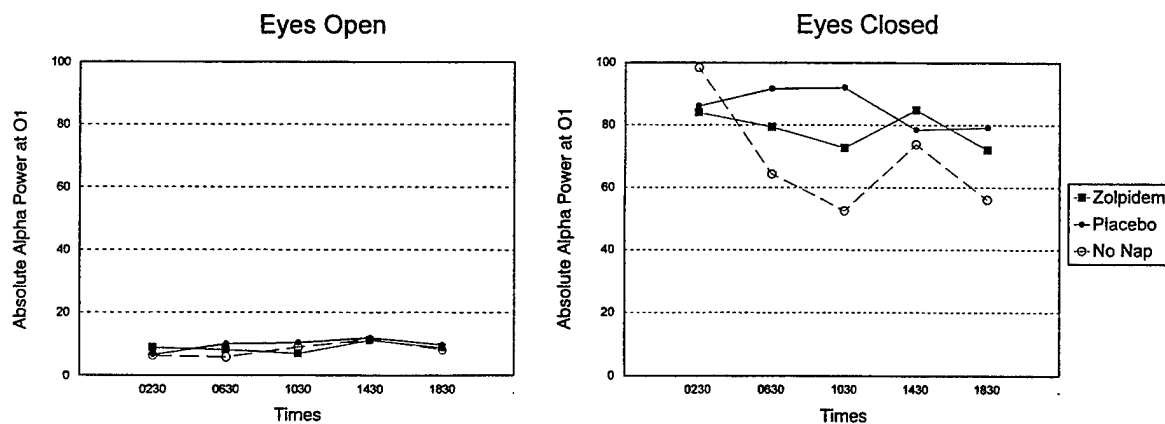


Figure 28. Effects of condition, time of day, and eye closure on alpha power at O1

There were 2-way interactions between time and eyes at O1 ($F(4,68)=3.15$, $p=.0195$) and O2 ($F(4,68)=3.44$, $p=.0128$), both of which were due to differences in the amount of alpha activity recorded at the various times of day under eyes closed, but not under eyes open ($p<.05$). Subsequent contrasts showed the effect at O1 under eyes closed was due to significantly more alpha at 0230 than at 0630, 1030, or 1830. The effect at O2 under eyes closed was similar except that there was more alpha at 0230 than at 1030, 1430, and 1830 (see figure 29). There also was a 2-way interaction between condition and time at O1 ($F(8,136)=2.20$, $p=.0314$), which was due to differences in alpha activity at the various times under the Nonap condition ($p<.05$), but not under the Znap and Pnap conditions. As shown in figure 30, there was more alpha activity at 0230 than at 1030 or 1830 under the Nonap condition.

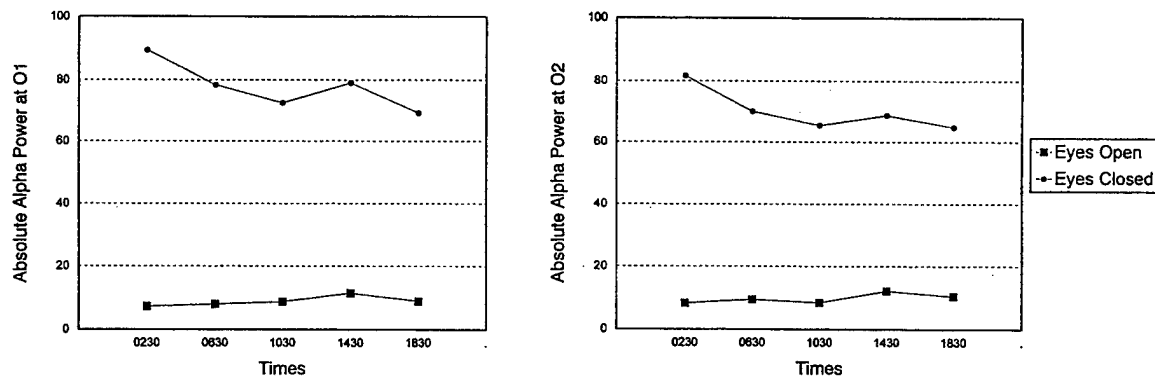


Figure 29. Effects of time of day and eye closure on alpha activity at O1 and O2

There were eyes main effects at every electrode site: Fz ($F(1,17)=35.83$, $p<.0001$), Cz ($F(1,17)=33.67$, $p<.0001$), C3 ($F(1,17)=38.55$, $p<.0001$), C4 ($F(1,17)=43.41$, $p<.0001$), Pz ($F(1,17)=41.33$, $p<.0001$), O1 ($F(1,17)=39.73$, $p<.0001$), O2 ($F(1,17)=44.02$, $p<.0001$). All of these were due to substantial increases in alpha activity under eyes closed in comparison to eyes open.

There were main effects on the condition factor at O1 ($F(2,34)=4.50$, $p=.0185$) and O2 ($F(2,34)=3.32$, $p=.0483$), both of which were due to the fact that alpha activity was greater after Pnap than after Nonap ($p<.05$). Although there was a tendency toward greater alpha activity under Znap as well ($p=.09$), the difference between Znap and Nonap was not significant (see figure 31).

Beta

The ANOVA on beta activity indicated a condition-by-eyes interaction at O1 ($F(2,34)=3.88$, $p=.0304$) which was due to the fact that, although there were differences between eyes open and eyes closed under each condition ($p<.05$), the difference was

most pronounced after Znap and least pronounced after Nonap. The Pnap condition was in between the other two (see figure 32).

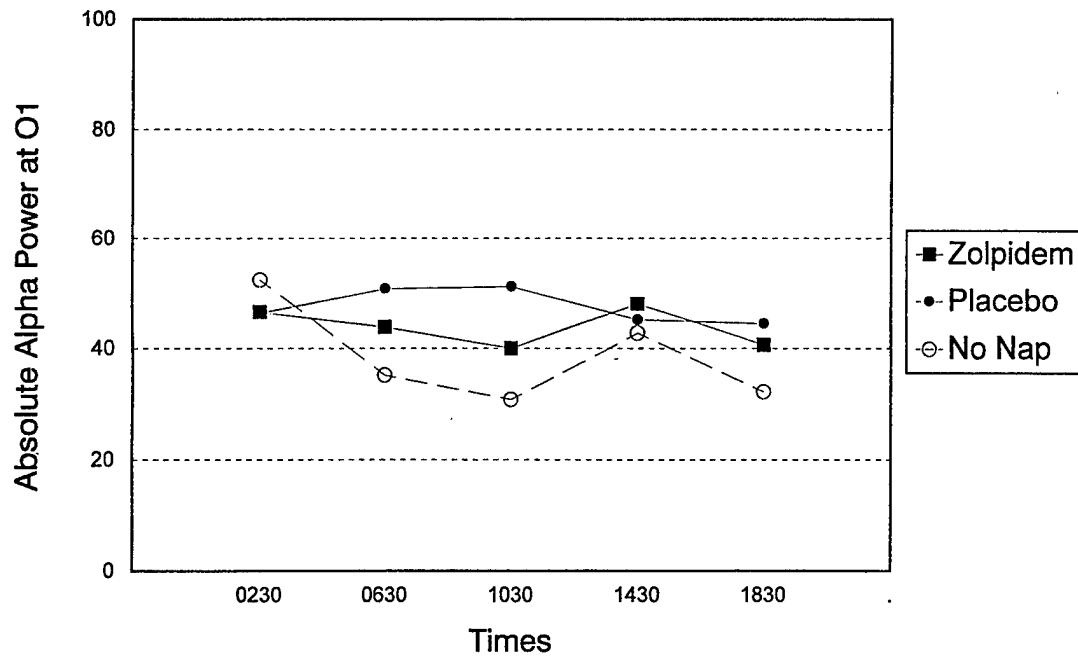


Figure 30. Effects of condition and time of day on alpha activity at O1

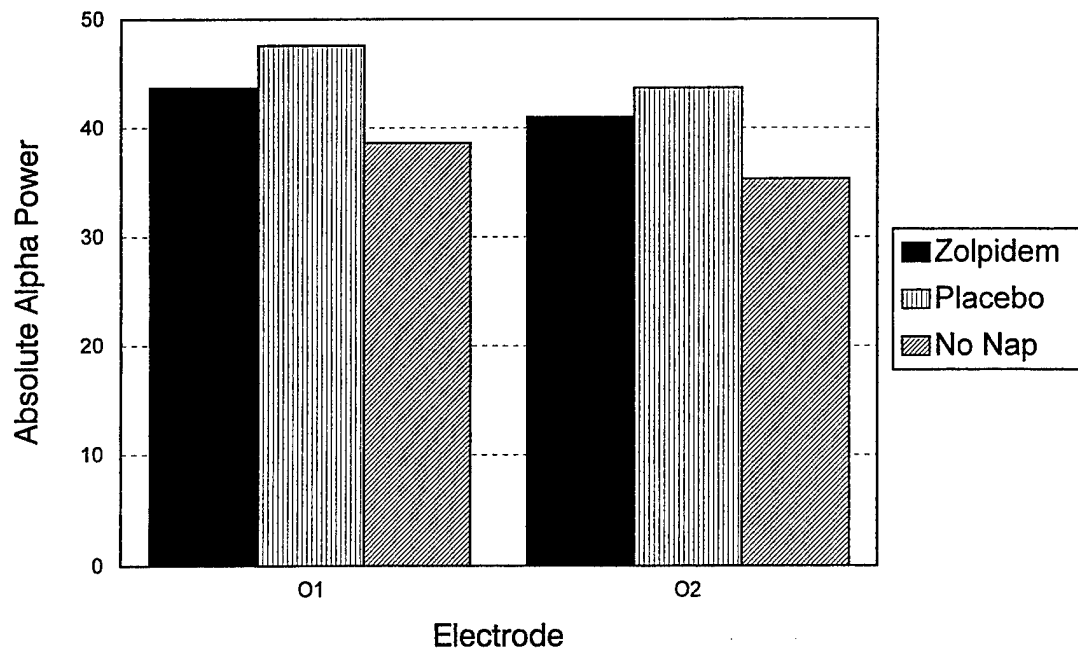


Figure 31. Effects of the three conditions on alpha activity at O1 and O2

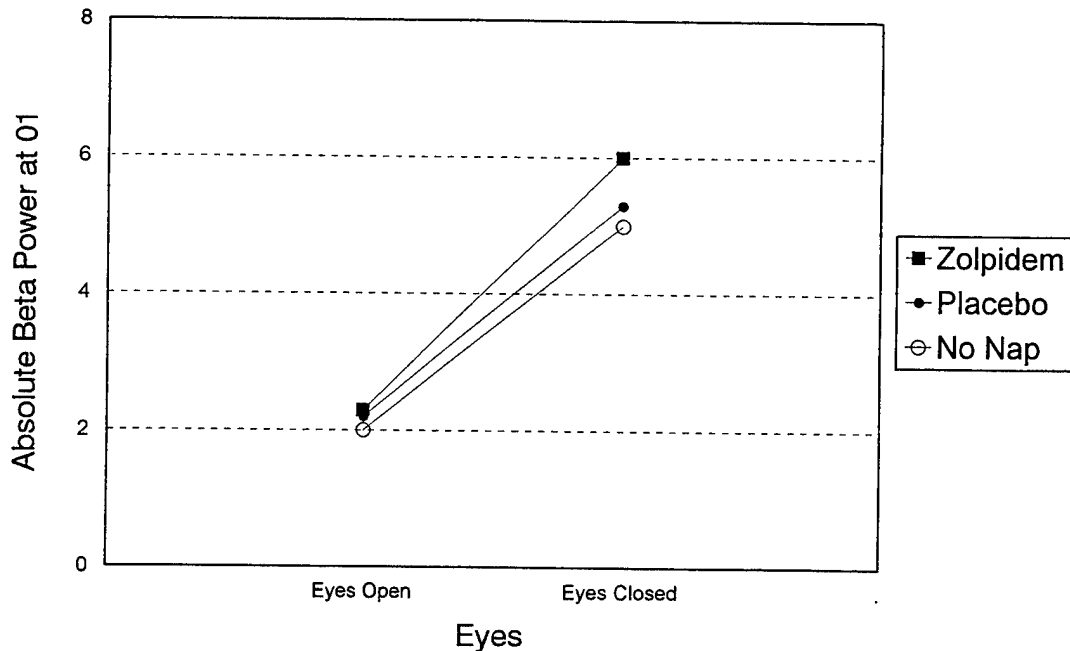


Figure 32. Effects of condition and eye closure on beta activity at O1

There were several main effects on both the eyes factor and the condition factor. The eyes main effects occurred at Fz ($F(1,17)=46.95$, $p<.0001$), Cz ($F(1,17)=53.79$, $p<.0001$), C3 ($F(1,17)=51.09$, $p<.0001$), C4 ($F(1,17)=57.25$, $p<.0001$), Pz ($F(1,17)=61.31$, $p<.0001$), O1 ($F(1,17)=65.20$, $p<.0001$), and O2 ($F(1,17)=59.52$, $p<.0001$). In each case, there was more beta activity under eyes closed than under eyes open. The condition main effects were found at C4 ($F(2,34)=4.48$, $p=.0188$), Pz ($F(2,34)=9.26$, $p=.0006$), and O1 ($F(2,34)=6.69$, $p=.0036$). At all three electrodes, there was significantly more beta activity after Znap than after Nonap ($p<.05$); and at Pz and O1, there was more beta after Pnap than after Nonap as well (see figure 33).

Desktop flight simulation task

The summary score from each simulation task was analyzed with a 3 by 5 repeated measures ANOVA for condition (Znap, Pnap, and Nonap) and time (0330, 0730, 1130, 1530, and 1930). The analysis on these data indicated only a slight tendency ($p=.09$) towards a time main effect, but this was not significant. There was no significant interaction between condition and time, and there was no condition main effect.

Vital signs

Vital signs data consisting of temperature, pulse, respiration, and blood pressure (systolic and diastolic) were analyzed with a repeated-measures ANOVA for condition

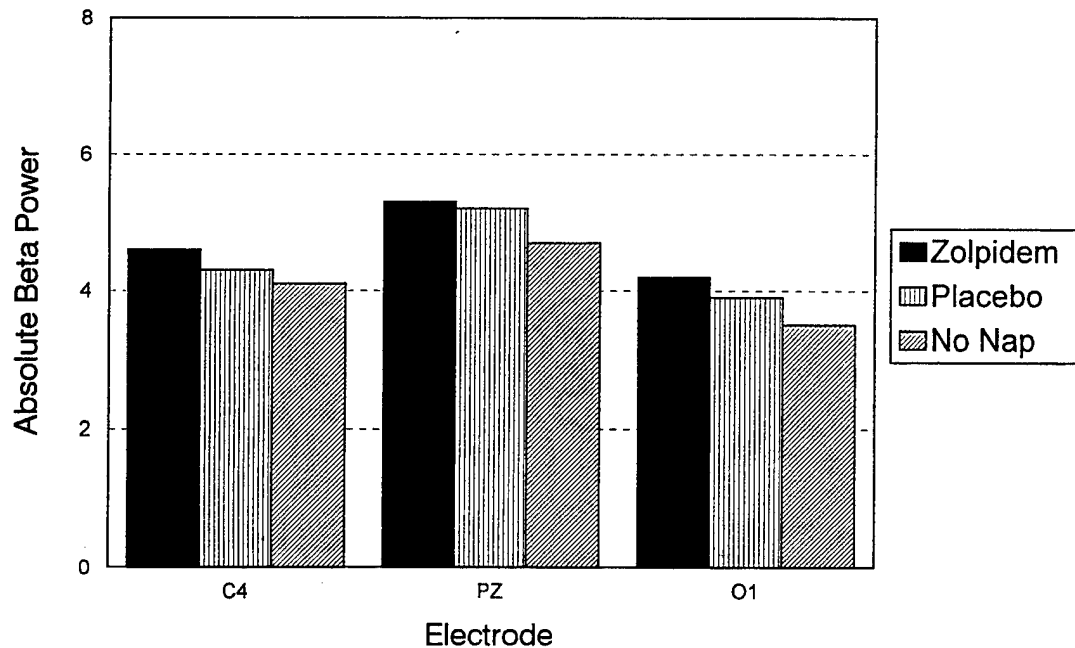


Figure 33. Effects of the three conditions on beta activity at C4, Pz, and O1

(Znap, Pnap, and Nonap) and time (0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, 1800, 2000, and 2135). The ANOVA indicated that none of the interventions (Znap, Pnap, or Nonap) had a significant effect on vital signs. However, there were changes in every measure, with the exception of diastolic blood pressure, as a function of time of day. As can be seen in figure 34, the time effect on oral temperature ($F(10,170)=24.35$, $p<.0001$) was due to a drop in temperature from 0400 to 0800 followed by a rise which attained statistical significance at 1600, 1800, 2000, and 2135 ($p<.05$). The time main effect on pulse rate ($F(10,170)=2.61$, $p=.0056$) was attributable to a drop in pulse from 0200 to 0800, followed by a rise in pulse from 0800 in comparison to the rates at 1000, 1400, 1600, and 2135 ($p<.05$). This effect is shown in figure 34. The time effect on respiration ($F(10,170)=2.29$, $p=.0152$) was due to an increase between 0200 and 1200; an increase between 0400 and 1200, 1400, and 1600; and an increase between 0800 and 1200, 1400, and 1600 ($p<.05$). Conversely, there was a decrease in respiration from 1200 to 2000 and from 1200 to 2135 ($p<.05$). This effect on respiration can be seen in figure 34. The time main effect on systolic blood pressure ($F(10,170)=2.32$, $p=.0141$), was because of higher pressure at 2000 and 2135 than at 0200, 0400, 0600, 0800, 1000, and 1400 ($p<.05$). In addition, systolic pressure increased between 0200 and 1800 (see figure 34).

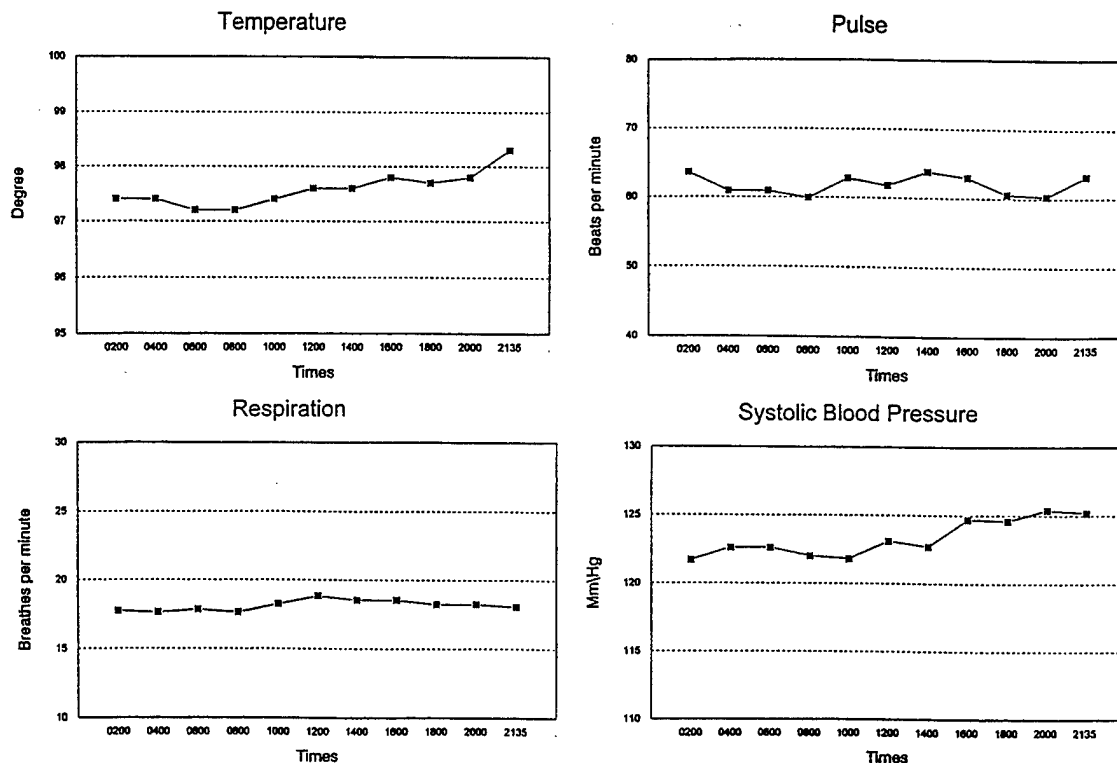


Figure 34. Effect of time of day on vital signs

Polysomnography

The data from the Znaps and the Pnaps were analyzed with a one-way repeated measures ANOVA. The variables were minutes in bed; minutes until sleep onset; total minutes of sleep; the percentage of stages 1, 2, 3, 4, and rapid eye movement (REM) sleep; the percentage of time awake after sleep onset; and the percentage of movement time during sleep. These data were analyzed in two ways because one subject was completely unable to sleep during his zolpidem nap (on the second night of the study) despite the fact that he was able to sleep during his placebo nap (on the fourth night). First, this subject's data were included with the sleep onset time set to 120.0 minutes, the time awake set to 120.0 minutes, the time asleep and all of the sleep stages set to 0.0, and the percentage of time awake set to 100 percent. Second, this subject's data were entirely excluded from the analysis.

The first ANOVA indicated main effects on the number of minutes to sleep onset ($F(1,17)=5.12$, $p=.0370$), the total minutes of sleep ($F(1,17)=7.95$, $p=.0118$), and the percentage of stage 1 sleep ($F(1,17)=5.87$, $p=.0269$). These resulted from the fact that sleep occurred faster (24 versus 46 minutes), lasted longer (101 versus 73 minutes),

and was more restful (8 versus 11 percent stage 1) after zolpidem tartrate than after placebo. The second ANOVA (with the problem subject excluded) indicated that there were main effects on the number of minutes until sleep onset ($F(1,16)=19.04$, $p=.0005$), the total minutes of sleep ($F(1,16)=26.41$, $p=.0001$), the percentage of stage 1 sleep ($F(1,16)=4.48$, $p=.0504$), and the percentage of stage 4 sleep ($F(1,16)=5.57$, $p=.0314$). As can be seen in figure 35, sleep was initiated faster and was more restful (less stage 1 and more stage 4) after zolpidem tartrate than after placebo.

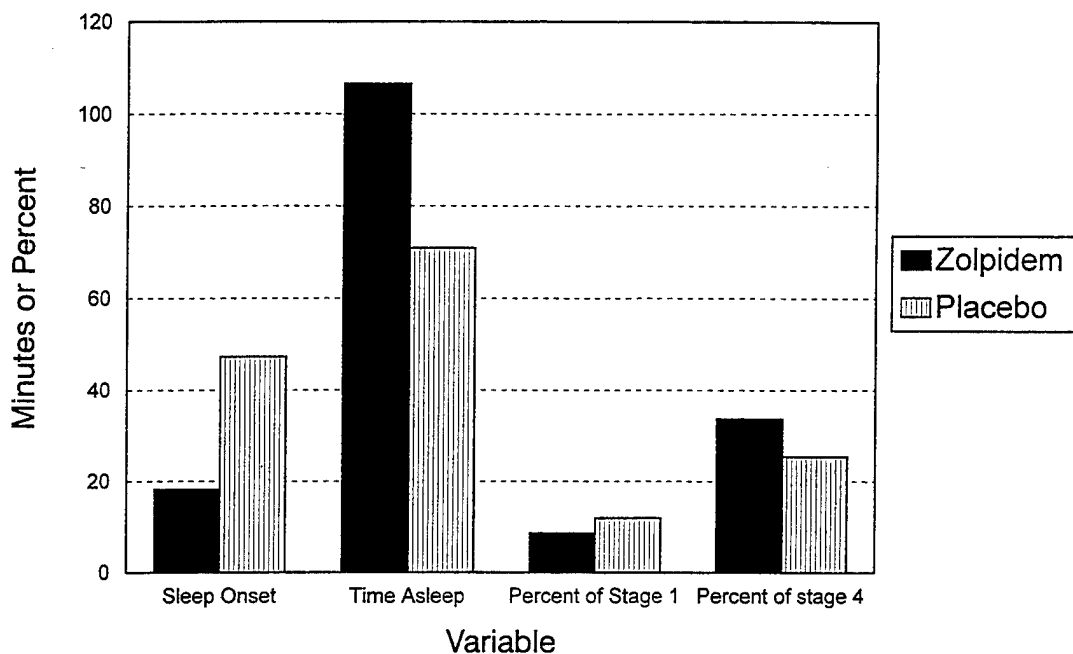


Figure 35. Effects of the three conditions on polysomnographic measures

Discussion

The present study evaluated the effectiveness of two types of 2-hour naps, placed prior to sleep deprivation, for sustaining the alertness of subjects during the final 24 hours of a 38-hour period of continuous wakefulness. In general, both types of naps (one induced with 10-mg zolpidem tartrate and the other a "natural", or placebo, nap) were superior to a forced-rest condition in which no nap was allowed. This is consistent with findings by Lubin et al. (1976) that bedrest is not a substitute for sleep. In addition, the zolpidem-induced nap was better than the placebo nap in several instances.

MMPI

Prior to discussing drug- and/or nap-related effects, it should be noted that the MMPI data collected from each volunteer in this investigation indicated that the present subjects were not markedly different from conventional aviators who tend towards

personal defensiveness, extroversion, denial of problems, nonconformity, high energy and activity, friendliness, and sociability (Caldwell et al., 1993). Thus, it seems that this sample of participants was representative of the larger population of general Army aviators.

Mood evaluation

In terms of the effectiveness of the napping interventions, POMS data revealed the nap induced with zolpidem tartrate was clearly better at sustaining subjective feelings of vigor than the forced-rest condition and slightly better than the placebo nap. The differences were most pronounced from 0500 to 0900 during the sleep deprivation period since these were the times when alertness suffered most under the no-nap condition. The fact that napping improved self-ratings of vigor is consistent with a report by Bonnet (1991) that a 200-minute nap effectively attenuated the reductions in vigor that occurred when subjects were deprived of the opportunity to sleep. Fatigue ratings in the present study also were lower after the zolpidem nap than after the forced-rest condition, whereas the placebo nap produced only marginally lower fatigue scores ($p=.07$). These results partially support the existing literature which indicates that prophylactic naps provide an effective countermeasure for sleep deprivation (Dinges, 1992). It is noteworthy that the full benefit of naps on subjective mood ratings were most apparent when the nap was facilitated by zolpidem tartrate.

Sleepiness evaluations

Feelings of alertness, energy, and sleepiness were measured both subjectively and objectively. For the subjective measure, a specially constructed self-report scale (the VAS) was used, and for the objective measure, a polysomnographic technique (the RTSW) was employed.

The VAS indicated subjects experienced significantly larger decrements in alertness and energy coupled with greater increases in both irritability and sleepiness under the forced-rest condition than under one or both napping conditions. After rest only, the loss of alertness persisted from 0400 to 1100, and the low energy, increased sleepiness, and elevated irritability lasted from 0400 to 0800. Feelings of talkativeness likewise dropped at 0500 and 0700 when napping was not used. Sleepiness ratings later in the day (from 1400 to 2000) were significantly larger under the forced-rest condition than after the napping conditions. A similar effect was found in alertness at 2000. Overall, there were 30 significant effects (e.g., differences among conditions at various times) on the VAS data from 0200 until 2000. Ninety-seven percent resulted because the zolpidem-induced nap was better than forced rest, and 63 percent resulted because the placebo nap was better than forced rest. Sixteen percent were due to better VAS ratings after the zolpidem nap than after the placebo nap. Thus, it is clear that naps were superior to rest alone in terms of sustaining subjective feelings of

alertness during sleep deprivation; however, it is also evident the maximum benefits from napping were greatest when zolpidem was administered.

The findings that VAS ratings of alertness and sleepiness were improved by napping in comparison to total sleep deprivation are at odds with one previous study (Dinges et al., 1987) in which it was reported that 2-hour naps did not improve self-reports of sleepiness despite the fact that objectively-measured performance declines were attenuated. This discrepancy may have resulted from the fact that Dinges et al. (1987) relied on the Stanford Sleepiness Scale (SSS) instead of the VAS. The SSS forces subjects to classify their states of alertness into 1 of 7 categories, whereas the VAS (used in this study) permits subjects to more freely define their feelings by placing a mark anywhere along a 100 mm line. The present findings are consistent with those of Bonnet (1991), who found that self-reports of vigor were improved by a 200-minute nap in comparison to a no-nap condition.

The VAS ratings also were consistent with physiologically-measured tendencies toward sleepiness. The RTSWs indicated subjects were able to remain awake longer after the zolpidem nap than after either the placebo nap or the rest-only intervention throughout the sleep-deprivation period. An examination of the overall means (collapsed across time of day) showed that prior to sleep deprivation, subjects were able to remain awake during the RTSW for approximately 17.7 minutes. During sleep deprivation (the last 21 hours of continuous wakefulness), subjects were able to remain awake for an average of only 11.7 minutes after the zolpidem nap, 9.4 minutes after the placebo nap, and only 6.3 minutes after forced rest. A further examination of individual RTSWs throughout the sleep-deprivation day showed the forced-rest condition to be inferior to one or both napping conditions at every time from 0210 until 2010. These findings are generally consistent with those of Sugerman and Walsh (1989) who reported longer sleep latencies (i.e., greater alertness) at several intervals following a 3.5-hour nap in comparison to sleep latencies after continuous wakefulness.

With regard to the relative efficacy of the zolpidem versus placebo naps, it appeared the zolpidem naps were superior. Sleepiness was less after the zolpidem nap in comparison to forced rest during 100 percent of the RTSWs; less after the placebo nap than after forced rest in 80 percent; and less after the zolpidem nap than after the placebo nap in 50 percent of the RTSWs.

Unfortunately, the benefits from napping were not apparent immediately after subjects were awakened. The VAS data collected at 2300 (about 5 minutes after awakening from the 2-hour naps) revealed feelings of alertness, energy, confidence, and talkativeness were lower after both the zolpidem and placebo naps than after the forced-rest condition. In addition, ratings of irritability and sleepiness were higher after both naps than after forced rest. This sleep inertia effect is not surprising considering there is a host of literature which describes these transient impairments immediately

upon awakening from any sleep episode (Dinges, 1989). The present results indicated that all of these problems disappeared by the time of the next VAS (administered at 0100, about 2 hours after awakening from the naps), with the exception of the alertness decrement which persisted until, but not beyond, 0100. It is unclear whether performance would have suffered along with mood during these times because the first performance test was not given until 0110; however, it has been suggested that the mood disruptions caused by sleep inertia outlast the performance decrements (Naitoh and Angus, 1989).

It is interesting to note that while postnap sleep inertia might have been expected to be more severe after zolpidem administration (due to the drug's average 2.5-hour half life), this was not the case. Initially, there did appear to be a slight hangover effect on the ratings from several scales; however, none of these were statistically significant--results were consistent with those of Balkin et al. (1992) who reported no zolpidem-related problems even at peak drug-concentration times after a 20-mg dose. The fact that the problems associated with sleep inertia immediately after the naps did not persist for more than 2 hours postnap was evident from an examination of the first RTSW (at 0210) which revealed significantly greater alertness after both naps than after rest only. The mean sleep latencies at 0210 were 16.4 minutes after the zolpidem nap, 17.6 minutes after the placebo nap, and 10.6 minutes after forced rest.

Taken together, the results from the VAS and the RTSW provide substantial evidence that prophylactic naps are effective for the maintenance of alertness during sustained operations, especially between 0400 and 1100. Also, it appears that naps induced with zolpidem offer greater protection from some of the effects of sleep deprivation than "natural" naps. However, whether zolpidem-induced naps or natural naps are used, care must be taken to avoid the temporary problems associated with postnap sleep inertia by allowing personnel sufficient time to fully awaken from naps prior to returning to work. These findings are consistent with earlier reports that performance immediately following strategic naps often is impaired (Naitoh and Angus, 1989). Also, when zolpidem tartrate is used to initiate a 2-hour prophylactic nap, there may be some minor effects until approximately 5.5 hour postdose, although zolpidem does not synergistically worsen the temporary effects of sleep inertia to a statistically-significant degree.

Cognitive evaluations

Basic cognitive skills were assessed with two computerized tests. Both of these tests required subjects to time-share cognitive resources among several tasks simultaneously--an ability essential to flying an aircraft and performing a variety of other complex types of work. The first cognitive test (the MATB) was an aviation-oriented simulation which required subjects to engage in systems monitoring, fuel management, and radio management while tracking an unstable target. The second cognitive test

(the SYNWORK) was a more generic simulation task which required subjects to concurrently respond to memory probes and perform arithmetic calculations while monitoring both visual and auditory stimuli.

Performance on the MATB showed the effects of sleep deprivation were most severe at 0910 (the third MATB session during deprivation), especially under the forced-rest condition. Although performance on the fuel management task was not significantly affected, there were differences among the three intervention strategies in aspects of systems monitoring, radio management, and tracking. At the 0910 session, subjects were slower at responding to warning lights after both the placebo nap and the rest-only condition than after the zolpidem-induced nap, and subjects were slower at responding to unacceptable dial deviations after rest-only than after either napping intervention. The variability in responding to warning lights was higher after the rest-only condition than after the zolpidem nap. These effects were consistent with results from the tracking task in that errors at 0910 were significantly larger under the forced-rest condition than under the zolpidem-nap condition. In addition, tracking skill was poorer after the placebo nap than after the zolpidem nap. On the radio management task, reaction time was affected as well, but although there was a slight tendency for this to have occurred at 0910, the significant differences were found only at 1710 (the last session of the day). At this point in time, reaction times were faster under both the zolpidem and rest-only conditions than under the placebo condition. Considering all of these effects together, the napping conditions generally were superior to the rest-only condition in sustaining the performance of sleep deprived subjects, and the zolpidem nap often was better than the placebo nap.

Analysis of composite performance scores from the SYNWORK showed the greatest decrements due to sleep deprivation occurred at 0705 (the second SYNWORK session during deprivation). This was particularly the case with the arithmetic task in which performance under the rest-only condition tended to be lower than performance under both napping conditions at this time. On the memory task, the difference among the three interventions occurred later (at 1105), and was due to poorer performance after the placebo nap than after the zolpidem nap, while neither of these differed from the forced-rest condition. There also was an overall difference among the three conditions in the visual monitoring task due to lower performance after the forced-rest condition than after either of the naps. Visual inspection of these data suggested a nonsignificant tendency toward a condition-by-time interaction in which the greatest differences between the rest-only and the napping conditions occurred between 0700 and 1100.

Overall, the cognitive testing results suggest that performance suffers the most between about 0700 and 1100 after a single night of sleep deprivation, consistent with the mood and alertness decrements which were most severe at these times. However, strategic napping prior to sleep loss effectively attenuated many of the deprivation-

related problems, especially on tasks which required vigilance and rapid responding. These findings agree generally with those of Dinges et al. (1988) who reported that napping early during 54 hours of sustained operations improved several aspects of cognitive performance, especially at approximately 0600. The present findings also support those of Bonnet (1991) who found that a 200-minute nap improved visual vigilance at 0530 in comparison to a no-nap condition. In addition, the present investigation provided evidence that a nap induced by zolpidem tartrate tended to be superior to a "natural" nap.

Waking EEG evaluation

Resting eyes-open/eyes-closed EEG assessments were performed to provide further insight into objectively measured levels of physiological arousal. The literature published to date apparently has not examined the effects of prophylactic napping on resting EEG activity during subsequent sleep deprivation. In this investigation it was found there were marked increases in theta activity accompanied by significant decreases in alpha activity as a function of time of day (or amount of sleep deprivation). This finding is similar to earlier reports that sleep deprivation generally produces increased slow-wave EEG activity associated with reduced alertness (Pigeau, Heslegrave and Angus, 1987; Comperatore et al., 1993; Lorenzo et al., 1995). However, the effects of prophylactic napping on the EEG were not as robust as expected. Delta activity recorded from one midline electrode (Cz) was found to increase from the early morning to later in the day (especially at 1030) after rest-only in comparison to the napping conditions, but theta activity was apparently unaffected by any of the treatment interventions. Both napping conditions significantly attenuated the deprivation-related reductions in occipital alpha activity in comparison to the forced-rest condition in which alpha power dropped sharply from 0230 relative to 0630, 1030, and 1830. Also, the overall amount of alpha activity recorded from O1 and O2 was lower after forced rest than after the placebo nap, with a similar tendency after the zolpidem nap. These changes in alpha activity probably resulted from an increased sleep tendency after the forced-rest period, in comparison to the napping conditions, since alpha attenuation is associated with increased sleepiness. This effect is consistent with the findings from the RTSW and the VAS which showed that alertness decreased more rapidly after the rest-only condition than after either napping condition. There also were changes in beta activity which indicated the superiority of napping relative to rest only. Significantly more beta activity was recorded from C4, Pz, and O1 throughout the day after the zolpidem-induced nap than after forced rest. Also, there was more beta recorded from Pz and O1 after the placebo nap than after rest only. Thus, it appears that overall central nervous system (CNS) activation was significantly improved by napping in that high frequency (beta) EEG activity was more pronounced and decrements in slower alpha activity were less severe throughout the deprivation period after brief, prophylactic episodes of sleep. The fact that these differences were not more robust and widespread may have been due to large amounts of intra subject

variability or to the fact that the resting EEG evaluations were of very short duration (total time for each assessment was about 5 minutes).

Desktop flight simulation

The accuracy with which subjects “flew” a course using the Microsoft Flight Simulator was unaffected by the interventions implemented in this study. Even time-of-day main effects were absent, indicating that sleep deprivation did not significantly degrade performance on this test. The lack of sensitivity on the desktop simulation may have been related to the amount of time it takes for subjects to reach asymptotic performance; however, such an explanation is purely speculative at this point.

Vital signs

Temperature, pulse, respiration, and blood-pressure data were collected primarily for medical monitoring purposes. However, statistical analyses of these data indicated oral temperatures were lowest between 0400 and 1000 after which they increased steadily, pulse rates were reduced from 0400-0800 and again from 1800-2000, and respiration rates were lowest between 0200 and 0800 after which they increased and then subsequently dropped again from 1200-2000. Systolic blood pressure started out low in the morning and steadily increased throughout the day. Most of these changes are typical circadian effects. There were no significant differences on vital-signs as a function of the treatments under investigation; however, it is interesting to note that the most pronounced effects on mood and performance (collapsed across treatments) tended to coincide with the lowest oral temperatures, respiration rates, and blood pressures (and to some extent, the lowest pulse rates as well).

Polysomnography

The sleep architecture of both naps was evaluated to objectively determine the effects of drug administration on nap quality and to provide insight into possible reasons for differences in the alertness-sustaining value of zolpidem-induced versus “natural” naps. A couple of strategies were used to analyze these data because one subject was completely unable to sleep after zolpidem administration (on the second night of the study). This transient insomnia may have been due to the novelty of the research environment or anxieties about the upcoming sleep deprivation period. However, whatever the cause, in one analysis this subject’s data were set to the most unfavorable values (longest possible time to sleep onset, 100 percent scored as awake, etc.), and in another analysis, this subject’s data were excluded entirely. The results of both analyses showed that, for the entire group of subjects, sleep onset occurred more rapidly, the total amount of sleep was longer, and sleep was more restful (less stage 1) after zolpidem than after placebo. When the problem subject’s data were excluded entirely, the analysis further revealed that deep sleep (stage 4) was more pronounced

after zolpidem than after placebo. The findings with regard to sleep onset and total sleep time are consistent with earlier reports that 10-mg zolpidem shortens the time it takes to fall asleep and increases total sleep time (Lorizio et al., 1990; Merlotti et al., 1989). In addition, Blois et al. (1993) reported that zolpidem tended to reduce the amount of stage 1 sleep in comparison to placebo.

Since subjects were provided with only a 2-hour time period for each nap, the more rapid sleep onset after zolpidem compared to placebo provided significantly more sleep under the zolpidem condition. As a group (with all participants included), subjects fell asleep almost twice as fast after zolpidem tartrate (24 minutes to sleep onset) than after placebo (46 minutes to sleep onset), which provided them with an average of 101 versus 73 minutes of sleep in the respective conditions. The longer sleep duration coupled with the fact that sleep was more restful under zolpidem than under placebo (8 versus 11 percent stage 1, respectively) no doubt contributed to the mild superiority of the zolpidem nap in terms of sustaining mood, alertness, and performance. This explanation is consistent with research conducted by Bonnet (1991) and Lumley et al. (1986) which demonstrated that performance and alertness improved as a function of sleep duration.

Side effects

Before discussing the side effects associated with zolpidem tartrate administration, the reader is reminded that contrary to Searle's recommendations, the zolpidem used in this study was administered 30 minutes prior to lights out instead of immediately before bed time. This was done to allow the capsule in which the drug was placed for blinding purposes to dissolve (Searle would not provide placebo tablets for this investigation). It was estimated the capsule would dissolve approximately 20 minutes after ingestion and that an additional 10 minutes would be required for absorption of the drug itself. However, the capsule apparently dissolved more rapidly than expected since several subjects evidenced drug-related effects beginning about 10 minutes prior to bed time. It is probable that many of the side effects reported here would not have occurred had the subjects been administered zolpidem tartrate immediately prior to lights out.

There were three reports of sluggishness, three of feeling drunk, three of feeling dizzy or lightheaded, and two reports of euphoria immediately prior to the zolpidem-induced nap. One of the subjects who felt euphoric stated that he felt as if he had had an "out of body experience." Four volunteers were affected by the drug to the extent that they required physical assistance walking to their bedrooms (they suffered minor disorientation and degraded motor coordination). One volunteer experienced active visual and auditory hallucinations 20-30 minutes after zolpidem administration, and he reported that these continued into the napping period (this subject reached stage 2 sleep after 48 minutes in bed). Following the zolpidem nap there were two reports of stomach upset 4.5 hours postdrug, one report of heartburn 24.5 hours postdrug, and

one report of diarrhea 17 hours postdrug. After placebo administration, there was one report of upset stomach and two reports of headache (at 4.5, 13, and 23 hours respectively). The postnap side effects with 10 mg of zolpidem are partially consistent with those found by Balkin et al. (1992) in which one subject out of a group of ten experienced nausea and another complained of a headache. The occurrence of mild hallucinations in one of the subjects in the present study was disconcerting, but not particularly alarming since one of the Balkin et al. (1992) volunteers experienced similar problems after a 20-mg dose of the medication. The Physician's Desk Reference (1995) indicates that these side effects may occur, although infrequently, after zolpidem administration.

Zolpidem tartrate should indeed be administered according to the manufacturer's recommendations (i.e., immediately prior to bedtime). Although several subjects did not experience problems with the medication as it was given in this protocol, there were noticeable drug-related effects on others which could present significant safety concerns in certain contexts. For instance, it might be disastrous for an individual who is unknowingly sensitive to zolpidem to take the drug prior to driving home from work in an attempt to rapidly promote sleep once at home in bed. Because of zolpidem's rapid onset of action, such an individual conceivably could lose the capacity to drive within 10-15 minutes after taking this medication. Thus, the medication should not be taken until bedtime. However, the fact that zolpidem has such a rapid onset of action can be a significant benefit in situations such as the one investigated here where there is only a brief period available for sleep. When personnel find they have only 2 hours for a strategic nap, it is clear that zolpidem can maximize the effectiveness of that nap by rapidly inducing a restful sleep.

Summary and conclusions

The results of this investigation indicate that 2-hour prophylactic naps are beneficial in sustaining the mood, alertness, and performance of personnel throughout the final 24 hours of 38-hour periods of continuous wakefulness. This was the case even though the naps were placed only slightly beyond what Lavie (1986) has called the "forbidden zone" for sleep (or the time of day at which sleep is difficult to obtain). Self-ratings of vigor, alertness, energy, and talkativeness were significantly higher after one or both of the 2-hour naps than after 2-hour periods of forced rest (with no sleep). Conversely, self-ratings of fatigue, irritability, and sleepiness were substantially lower after the naps than after rest only. These subjective reports were reinforced by objective, physiological tests which indicated naps increased the subjects' abilities to maintain wakefulness in comparison to rest only. Mood and alertness decrements were most severe between 0400 and 1100. Cognitive test results often were consistent with the self-report and physiological data, although many aspects of cognitive functioning were unaffected by sleep deprivation. For example, subjects seemed to perform fuel

management, desktop flight simulation, and auditory monitoring about as well after total sleep deprivation as after the naps. However, subjects were much better able to monitor systems, respond to warning lights, manage radios, track targets, and perform mental calculations after napping than after rest only, especially between 0700 and 1100.

These results show that prophylactic naps can effectively attenuate many of the decrements associated with sleep deprivation in continuous operations, especially in the mid-morning hours (some positive effects were seen late in the deprivation period as well). However, caution should be exercised scheduling personnel to return to duty within 3 hours following naps, at which time sleep inertia may increase feelings of sleepiness and irritability beyond the levels seen in workers who are totally sleep deprived. Although personnel are certainly not incapacitated by these problems, there will be a tendency toward discomfort and grogginess immediately after awakening (the same is true after awakening from a normal, 8-hour sleep period). After the 3-hour point, the benefits from napping should overshadow any early problems attributable to sleep inertia. Also, it may be possible to overcome some postnap grogginess with caffeine, but this remains to be determined in future studies.

An examination of the relative efficacy of the zolpidem-induced nap compared to the "natural" nap indicated the zolpidem nap often was superior, because subjects were able to fall asleep faster, remain asleep longer, and sleep more deeply after zolpidem than after placebo. There were very slight indications that zolpidem contributed to postnap sleep inertia, but it is doubtful that zolpidem will create mood or performance impairments in the operational environment. Other investigators have reported that even a 20-mg dose of zolpidem (twice the dose used in this study) does not impair mood or performance when testing is performed as early as 1.5 hours postdose (Balkin et al., 1992). Thus, in situations where personnel are provided with only limited opportunities to sleep (which may occur at less than optimal times in the circadian phase), zolpidem administration should be strongly considered. However, zolpidem should only be administered immediately prior to the sleep period because of its rapid onset of action. Also, personnel who will use this medication in operational scenarios should be administered at least one test dose prior to deployment to check for idiosyncratic drug reactions. Finally, our data suggest that a conservative grounding period for aviators following zolpidem administration would be 6 hours (as opposed to the current 12-hour rule), although it is quite possible that a shorter amount of time probably would be sufficient. Future work will explore the grounding issue further.

References

- Akerstedt, T., and Torsvall, L. 1985. Napping in shift work. Sleep, 8(2):105-109.
- Ascalone, V., Flaminio, L., Guinebault, P., Thenot, J. P., and Morselli, P. L. 1992. Determination of zolpidem, a new sleep-inducing agent, and its metabolites in biological fluids: pharmacokinetics, drug metabolism and overdosing investigations in humans. Journal of chromatography, 581:237-250.
- Balkin, T. J., O'Donnell, V. M., Wesensten, N., McCann, U., and Belenky, G. 1992. Comparison of the daytime sleep and performance effects of zolpidem versus triazolam. Psychopharmacology, 107:83-88.
- Bartholini, G. 1988. Growing aspects of hypnotic drugs. In J.P. Sauvanet, S.Z. Langer, and P.L. Morselli (Eds.) Imidazopyridines in sleep disorders, pp. 1-9. New York: Raven Press.
- Bensimon, G., Foret, J., Warot, D., Lacomblez, L., Thiercelin, J. F., and Simon, P. 1990. Daytime wakefulness following a bedtime oral dose of zolpidem 20 mg, flunitrazepam 2 mg and placebo. British journal of clinical pharmacology, 30:463-469.
- Bianchetti, G., Dubruc, C., Thiercelin, J. F., Bercoff, E., Bouchet, J. L., Emeriau, J. P., Galperine, I., Lambert, D., Vandel, B., and Thebault, J. J. 1988. Clinical pharmacokinetics of zolpidem in various physiological and pathological conditions. In J. P. Sauvanet, S. Z. Langer, and P. L. Morselli (Eds.), Imidazopyridines in sleep disorders, pp. 155-163. New York: Raven Press.
- Blois, R., Gaillard, J., Attali, P., and Coquelin, J. 1993. Effect of zolpidem on sleep in healthy subjects: A placebo controlled trial with polysomnographic recordings. Clinical therapeutics, 15(5):797-809.
- Bonnet, M. H. 1990. Dealing with shift work: physical fitness, temperature, and napping. Work and stress, 4(3):261-274.
- Bonnet, M. H. 1991. The effect of varying prophylactic naps on performance, alertness and mood throughout a 52-hour continuous operation. Sleep, 14(4):307-315.
- Caldwell, J. A., O'Hara, C., Caldwell, J. L., Stephens, R. L., and Krueger, D. P. 1993. Personality profiles of U.S. Army helicopter pilots screened for special operations duty. Military psychology, 5(3):187-199.

- Carskadon, M. A., and Dement, W. C. 1982. Nocturnal determinants of daytime sleepiness. Sleep, 14(4):307-315.
- Comperatore, C. A., Caldwell, J. A., Stephens, R. L., Mattingly, A., Chiaramonte, J., and Trast, S. T. 1993. The use of electrophysiological and cognitive variables in the assessment of degradation during periods of sustained wakefulness. Fort Rucker, AL: U.S. Army Aeromedical Research Laboratory. USAARL Report No. 93-5.
- Dinges, D. F. 1992. Adult napping and its effects on ability to function, In C. Stampi (Ed.), Why we nap: Evolution, chronobiology, and functions of polyphasic and ultrashort sleep, 119-134. Boston: Birkhäuser.
- Dinges, D. F. 1986. Differential effects of prior wakefulness and circadian phase on nap sleep. Electroencephalography and clinical neurophysiology, 64:224-227.
- Dinges, D. F. 1989. Napping patterns and effects in human adults, in D. F. Dinges and R. J. Broughton (Eds.) Sleep and alertness: Chronobiological, behavioral, and medical aspects of napping, 171-204. New York: Raven Press.
- Dinges, D. F., Orne, M. T., and Orne, E. C. 1985. Assessing performance upon abrupt awakening from naps during quasi-continuous operations. Behavior research methods, instruments, & computers, 17(1):37-45.
- Dinges, D. F., Orne, M. T., Whitehouse, W. G., and Orne, E. C. 1987. Temporal placement of a nap for alertness: Contributions of circadian phase and prior wakefulness. Sleep, 10(4):313-329.
- Dinges, D. F., Whitehouse, W. G., Orne, E. C., and Orne, M. T. 1988. The benefits of a nap during prolonged work and wakefulness. Work & stress, 2(2):139-153.
- Elsmore, T. F. 1991. A synthetic work environment for the PC (Version 2.0). Unpublished user manual. Washington, DC: Office of Military Performance Assessment Technology, Walter Reed Army Institute of Research.
- Friedmann, J. Ch., and Prenez, A. 1988. Safety evaluation of zolpidem. In J. P. Sauvanet, S. Z. Langer, and P. L. Morselli (Eds.) Imidazopyridines in sleep disorders, pp. 123-138. New York: Raven Press.
- George, P., Rossey, G., Depoortere, B., Mompon, B., Allen, J., and Wick, A.. 1988. Zolpidem and related compounds: syntheses, physical properties and structure-activity relationships. In J. P. Sauvanet, S. Z. Langer, and P. L. Morselli (Eds.) Imidazopyridines in sleep disorders, pp. 11-23. New York: Raven Press.

- Gillberg, M. 1984. The effects of two alternative timings of a one-hour nap on early morning performance. Biological psychology, 19:45-54.
- Hartse, K. M., Roth, T., and Zorick, F. J. 1982. Daytime sleepiness and daytime wakefulness: the effect of instruction. Sleep, 5:S107-S118.
- Haslam, D. R. 1985. Sleep deprivation and naps. Behavior research methods, instruments, & computers, 17(1):46-54.
- Kryger, M. H., Steljes, D., Pouliot, Z., Neufeld, H. and Odynski, T. 1991. Subjective versus objective evaluation of hypnotic efficacy: experience with zolpidem. Sleep, 14(5):399-407.
- Langer, S. Z., Arbilla, S., Scatton, B., Niddam, R., and Dubois, A.. 1988. Receptors involved in the mechanism of action of zolpidem. In J. P. Sauvanet, S. Z. Langer, and P. L. Morselli (Eds.) Imidazopyridines in sleep disorders, pp. 55-70. New York: Raven Press.
- Lavie, P. 1986. Ultrashort sleep-waking schedule. III. "Gates" and "forbidden zones" for sleep. Electroencephalography and clinical neurophysiology, 63:414-425.
- Lavie, P., and Weler, B. 1989. Timing of naps: Effects on post-nap sleepiness levels. Electroencephalography and clinical neurophysiology, 72:218-224.
- Lorenzo, I., Ramos, C. A., Guevara, M. A., and Corsi-Cabrera, M. 1995. Effect of total sleep deprivation on reaction time and waking EEG activity in man. Sleep, 18(5):346-354.
- Lorizio, A., Terzano, M., Parrino, L., Cesana, B., and Priore, P. 1990. Zolpidem: a double-blind comparison of the hypnotic activity and safety of a 10-mg versus 20-mg dose. Current therapeutic research, 47(5):889-898.
- Lubin, A., Hord, D. J., Tracy, M. L., and Johnson, L. C. 1976. Effects of exercise, bedrest and napping on performance decrement during 40 hours. Psychophysiology, 13(4):334-339.
- Lumley, M., Roehrs, T., Zorick, F., Lamphere, J., and Roth, T. 1986. The alerting effects of naps in sleep-deprived subjects. Psychophysiology, 23(4):403-408.
- Matsumoto, K. 1981. Effects of nighttime naps on body temperature changes, sleep patterns, and self-evaluation of sleep. Journal of human ergology, 10:173-184.

- Matsumoto, K., and Harada, M. 1994. The effect of night-time naps on recovery from fatigue following night work. Ergonomics, 37(5): 899-907.
- McNair, D. M., Lorr, M., and Droppleman, L. F. 1981. Manual for the profile of mood states. San Diego: Educational and Industrial Testing Service.
- Merlotti, L., Roehrs, T., Koshorek, G., Zorick, F., Lamphere, J., and Roth, T. 1989. The dose effects of zolpidem on the sleep of healthy normals. Journal of clinical psychopharmacology, 9(1):9-14.
- Mullaney, D. J., Kripke, D. F., Fleck, P. A., and Johnson, L. C. 1983. Sleep loss and nap effects on sustained continuous performance. Psychophysiology, 20(6):643-651.
- Naitoh, P., and Angus, R. G. 1989. Napping and human functioning during prolonged work. In D.F. Dinges and R.J. Broughton (Eds.), Sleep and alertness: chronobiological, behavioral, and medical aspects of napping, pp. 221-246. New York: Raven Press, Ltd..
- Naitoh, P., Englund, C. E., and Ryman, D. 1982. Restorative power of naps in designing continuous work schedules. Journal of human ergology, 11(Suppl):259-278.
- Nicholson, A. N., and Pascoe, P. A. 1986. Hypnotic activity of an imidazo-pyridine (zolpidem). British journal of clinical pharmacology, 21:205-211.
- Nicholson, A. N., Pascoe, P. A., Roehrs, T., Roth, T., Spencer, M. B., Stone, B. M., and Zorick, F. 1985. Sustained performance with short evening and morning sleeps. Aviation, space and environmental medicine, 56:105-114.
- Palminteri, R. and Narbonne, G. 1988. Safety profile of zolpidem. In J.P. Sauvanet, S.Z. Langer, and P.L. Morselli (Eds.) Imidazopyridines in sleep disorders, pp 351-360. New York: Raven Press.
- Penetar, D., McCann, U., Thorne, D., Kamimori, G., Galinski, C., Sing, H., Thomas, M., and Belenky, G. (1993). Caffeine reversal of sleep deprivation effects on alertness and mood. Pharmacology, 112:359-365.
- Physician' Desk Reference. 1995. Ambien (brand of zolpidem tartrate), pp 2304-2307. Oradell, NJ: Medical Economics Co., Inc.

- Pigeau, R. A., Heselegrave, R. J., and Angus, R. G. 1987. Psychophysiological measures of drowsiness as estimators of mental fatigue and performance degradation during sleep deprivation. In Electric and magnetic activity of the central nervous system: Research and clinical applications in aerospace medicine. AGARD CP-432, 21-1/21-16. Neuilly sur Seine, France: Advisory Group for Aerospace Research and Development.
- Quera-Salva, M. A., McCann, C., Boudet, J., Frisk, M., Borderies, P., and Meyer, P. 1994. Effects of zolpidem on sleep architecture, night time ventilation, daytime vigilance and performance in heavy snorers. British journal of clinical pharmacology, 37:539-543.
- Rechtschaffen, A., and Kales, A. 1968. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Washington, DC: U.S. Government Printing Office.
- Richens, A., Mercer, A. J., Jones, D. M., Griffiths, A., and Marshall, R. W. 1993. Effects of zolpidem on saccadic eye movements and psychomotor performance: a double-blind, placebo controlled study in healthy volunteers. British journal of clinical pharmacology, 36:61-65.
- Rogers, A. S., Spencer, M. B., Stone, B. M., and Nicholson, A. N. 1989. The influence of a 1 h nap on performance overnight. Ergonomics, 32(10):1193-1205.
- Rosa, R.R. 1993. Napping at home and alertness on the job in rotating shift workers. Sleep, 16(8):727-735.
- Sanger, D. J., Perrault, G., Morel, E., Joly, D., and Zivkovic, B. 1987. The behavioral profile of zolpidem, a novel hypnotic drug of imidazopyridine structure. Physiology and behavior, 41:235-240.
- Scharf, M. B., Kaffeman, M., Rodgers, L., and Segal, J. 1988. Single dose tolerance study of zolpidem. In J. P. Sauvanet, S. Z. Langer, and P. L. Morselli (Eds.) Imidazopyridines in sleep disorders, pp. 175-181. New York: Raven Press.
- Schweitzer, P. K., Muehlback, M. J., and Walsh, J. K. 1992. Countermeasures for night work performance deficits: The effect of napping or caffeine on continuous performance at night. Work & stress, 6(4):355-365.
- Sicard, B. A., Troucherie, S., Moreau, J., Vielillefond, H., and Court, L.A. 1993. Evaluation of zolpidem on alertness and psychomotor abilities among aviation ground personnel and pilots. Aviation, space, and environmental medicine, 64:371-375.

and metabolism of zolpidem in various animal species and in humans. In J.P. Sauvanet, S.Z. Langer, and P.L. Morselli (Eds.). Imidazopyridines in sleep disorders, pp 139-153. New York: Raven Press.

Webb, W. 1987. The proximal effects of two and four hour naps within extended performance without sleep. Psychophysiology, 24(4):426-429.

Appendix

Manufacturer's list

Cadwell Laboratories
909 North Kellogg Street
Kennewick, WA 99336

Nihon Kohden
17112 Armstrong Avenue
Irvine, CA 92714

CH Products
970 Park Center Drive
Vista, CA 92083

SensorMedics
22705 Savi Ranch Parkway
Yorba Linda, CA 92687

Coulbourn Instruments, Incorporated
Box 2551
Lehigh Valley, PA 18001

Critikon
4110-T George Road
Tampa, FL 33614

Digital Equipment Corporation
P.O. Box C52008
Nashua, NH 03061-2008

Grass Instrument Company
101 Old Colony Avenue
Quincy, MA 02169

IVAC Corporation
10200 Campus Point Drive
San Diego, CA 92121

Lafayette Instrument Company
Lafayette, IN 47903

Marquette
8200 West Tower Avenue
Milwaukee, WI 53223

MicroSoft
1 Microsoft Way
Redmond, WA 98052